liposomes to the bottom phase.

5/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10748665 98246608 PMID: 9578605
The covalent coupling of Arg-Gly-Asp-containing peptides to **liposomes**: purification and biochemical function of the lipopeptide.
Gyongyossy-Issa MI; Muller W; Devine DV
Canadian Red Cross Society Blood Services, University of British Columbia, 4750 Oak Street, Vancouver, British Columbia, Canada. missa@unixg.ubc.ca
Archives of biochemistry and biophysics (UNITED STATES) May 1 **1998**, 353 (1) p101-8, ISSN 0003-9861 Journal Code: 6SK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
With the advent of **liposomes** as drug carriers, there arises a need for efficient targeted delivery in vivo. Proteins **coupled** to **liposomes** usually yield heterogeneous products that are ill-defined both chemically and in terms of spatial orientation. We now report on the disulfide linkage to the surface of intact **liposomes** of a peptide representing one-half of a ligand-receptor pair. An RGD-motif-containing peptide was **coupled** to the phospholipid PDP-DOPE of the **liposomes** by a **thiol** -disulfide exchange. The resulting lipopeptides were amenable to definition by TLC, HPLC, and MS and found to be in a functional orientation allowing biochemical interaction with their receptor, the integrin glycoprotein IIb-IIIa. Copyright 1998 Academic Press.

5/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09527394 97246568 PMID: 9092806
Membrane anchorage brings about fusogenic properties in a short synthetic peptide.
Pecheur EI; Hoekstra D; Sainte-Marie J; Maurin L; Bienvenue A; Philippot JR
UMR 5539 CNRS, Dynamique Moleculaire des Interactions Membranaires, Dept Biologie Sante, Universite Montpellier II, France. epecheur@univ-montp2.fr
Biochemistry (UNITED STATES) Apr 1 **1997**, 36 (13) p3773-81, ISSN 0006-2960 Journal Code: A0G
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The fusogenic properties of an amphipathic net-negative peptide (wae 11), consisting of 11 amino acid residues, were studied. We demonstrate that, whereas the free peptide displays no significant fusion activity, membrane fusion is strongly promoted when the peptide is anchored to a **liposomal** membrane. The fusion activity of the peptide appears to be independent of pH, and membrane merging is an essentially nonleaky process. Thus, the extents of lipid mixing and contents mixing were virtually indistinguishable. Vesicle aggregation is a prerequisite for fusion. For this process to take place, the target membranes required a positive charge which was provided by incorporating lysine-**coupled** phosphatidylethanolamine (PElys). The **coupled** peptide, present in one population, could thus cause vesicle aggregation via nonspecific electrostatic interaction with PElys. However, the free peptide failed to induce aggregation of PElys vesicles, suggesting that the spatial orientation of the **coupled** peptide codetermined its ability to bring about vesicle aggregation and fusion. With the monitoring of changes in the intrinsic Trp fluorescence, in conjunction with KI-quenching studies, it would appear that hydrophobic interactions facilitate the fusion event,

Record type: Completed

Several coupling methods for binding antibodies (Ab) to **liposomes** have previously been developed. We were interested in examining if some of these methods would be suitable for attaching Ab to long-circulating formulations of **liposomes** (SL), sterically stabilized with poly(ethylene glycol) (PEG). We studied three 'classical' coupling methods in which Ab was attached at the bilayer surface of SL, and two new coupling methods in which Ab was attached at the PEG terminus. Parameters examined including binding efficiency, antibody surface density, the ability of the immunoliposomes to remote-load the anticancer drug doxorubicin, and the specific binding of the resulting immunoliposomes to target cells. The non-covalent **biotin-avidin** coupling method resulted in low Ab densities at the cell surface, as did a coupling in method in which maleimide-derivatized Ab was attached to the **liposome** surface through a thiolated phospholipid incorporated into the **liposomes**. The low levels of Ab achieved in these method was likely due to interference by PEG with the access of the Ab to the **liposome** surface. However, when a maleimide-derivatized Ab was **coupled** to thiolated PEG, moving the coupling reaction away from the **liposome** surface, very high coupling efficiencies were achieved, and these immunoliposomes achieved good specific binding to their target cells. Oxidizing the Fc region of the Ab and coupling it to the PEG terminus through a hydrazone bond was a less efficient coupling method, but had the advantage of retaining Ab orientation. Efficient remote-loading of doxorubicin was found for immunoliposomes in which Ab was attached at the PEG terminus.

5/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09499372 95359183 PMID: 7632714

A new strategy for attachment of antibodies to sterically stabilized **liposomes** resulting in efficient targeting to cancer cells.

Allen TM; Brandeis E; Hansen CB; Kao GY; Zalipsky S

Department of Pharmacology, University of Alberta, Edmonton, Canada.

Biochimica et biophysica acta (NETHERLANDS) Jul 26 **1995**, 1237 (2) p99-108, ISSN 0006-3002 Journal Code: A0W

Erratum in Biochim Biophys Acta 1995 Dec 13;1240(2) 285

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The development of long-circulating formulations of **liposomes** (S-**liposomes**), sterically stabilized with lipid derivatives of poly(ethylene glycol) (PEG), has increased the likelihood that these **liposomes**, **coupled** to targeting ligands such as antibodies, could be used as drug carriers to deliver therapeutic drugs to specific target cell populations in vivo. We have developed a new methodology for attaching monoclonal antibodies to the terminus of PEG on S-**liposomes**. A new end-group functionalized PEG-lipid derivative pyridylthiopropionoylamino-PEG- distearoylphosphatidylethanolamine (PDP-PEG-DSPE) was synthesized for this purpose. Incorporation of PDP-PEG-DSPE into S-**liposomes** followed by mild thiolysis of the PDP groups resulted in formation of reactive **thiol** groups at the periphery of the lipid vesicles. Efficient attachment of maleimide-derivatized antibodies took place under mild conditions even when the content of the functionalized PEG-lipid in S-**liposomes** was below 1% of total lipid. The resulting S-immunoliposomes showed efficient drug remote loading, slow drug release rates and increased survival times in circulation compared to **liposomes** lacking PEG. When antibodies recognizing several different tumor-associated antigens were **coupled** to the PEG terminus of S-**liposomes** a significant increase in the in vitro binding of **liposomes** to the target cells was observed. The binding of S-immunoliposomes containing entrapped doxorubicin to their target cell population resulted in increased cytotoxicity compared to **liposomes** lacking the targeting antibody.

surface. METHODS. To achieve coupling of GUS to the **liposomes**, introduction of extra **thiol** groups was required. Two thiolating agents were examined: iminothiolane and SATA. RESULTS. When iminothiolane was used, aggregation of enzymosomes was observed above enzyme densities of 10 micrograms GUS/mumol lipid (TL). An increased electrostatic repulsion of the enzymosomes, created by inclusion of additional negatively charged lipids and by lowering the ionic strength of the external aqueous medium resulted in enzyme densities > or = 20 micrograms GUS/mumol TL without aggregation. Utilizing SATA, > or = 30 micrograms GUS/mumol TL could be coupled without aggregation, even at physiological ionic strength. It was shown that the enzyme density on immuno-enzymosomes, and thus on the tumor cell surface, strongly influences the antitumor effect of the prodrug daunorubicin-glucuronide against in vitro cultured ovarian cancer cells. The antitumor effect of immuno-enzymosomes with enzyme densities of about 20 micrograms GUS/mumol TL was similar to that of the parent drug daunorubicin. CONCLUSIONS. SATA-mediated thiolation of GUS-molecules enabled the preparation of immuno-enzymosomes with high enzyme densities while avoiding spontaneous aggregation. In vitro antitumor activity experiments showed that the improved immuno-enzymosome system is able to completely convert the prodrug daunorubicin-glucuronide into its parent compound.
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S3          1   S2 AND ANTHRACYCLIN?
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 5/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10752304   98384811   PMID: 9718699
   Aqueous two-phase affinity partitioning of biotinylated liposomes
 using neutral avidin as affinity ligand.
  Ekblad L; Kernbichler J; Jergil B
  Centre for Chemistry and Chemical Engineering, Lund University, Sweden.
  Journal of chromatography (NETHERLANDS)  Jul 31 1998,  815  (2)
 p189-95,   Journal Code: BXJ
  Languages: ENGLISH
  Document type: Journal Article
  Record type: Completed
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Biotinylated small unilamellar **liposomes** were affinity partitioned in an aqueous poly(ethylene glycol)-dextran two-phase system using **avidin coupled** to dextran as affinity ligand. In the absence of affinity ligand more than 90% of the **liposomes** partitioned in the poly(ethylene glycol)-rich top phase, whereas in its presence more than 95% partitioned in the dextran-rich bottom phase. For this redistribution to occur 10 mM and above of lithium sulphate, or other appropriate salts, had to be added to the two-phase system. Without added salt the **liposomes** with complexed **avidin**-dextran instead partitioned in the top phase. An extended mixing time for the system was required for maximum redistribution. Less than two **biotin** residues per **liposome**, **coupled** via a C6 spacer arm, was required to redistribute the

possibly involving (partial) peptide penetration. Such a penetration may be needed to trigger formation of a transient, nonbilayer structure. Since lysophosphatidylcholine inhibited while monoolein strongly stimulated peptide-induced fusion, our data indicate that wae 11-induced fusion proceeds according to a model consistent with the stalk-pore hypothesis for membrane fusion.

5/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09515617 96267507 PMID: 8710754
Immunoliposomes as enzyme-carriers (immuno-enzymosomes) for antibody-directed enzyme prodrug therapy (ADEPT): optimization of prodrug activating capacity.
Vingerhoeds MH; Haisma HJ; Belliot SO; Smit RH; Crommelin DJ; Storm G
Department of Pharmaceutics, Faculty of Pharmacy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, The Netherlands.
Pharmaceutical research (UNITED STATES) Apr **1996**, 13 (4) p604-10, ISSN 0724-8741 Journal Code: PHS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
PURPOSE. Immuno-enzymosomes are tumor-specific immunoliposomes bearing enzymes on their surface. These enzymes are capable of converting relatively nontoxic prodrugs into active cytostatic agents. The enzyme beta-glucuronidase (GUS)4 was **coupled** to the external surface of immunoliposomes directed against ovarian carcinoma cells. This study aimed at optimization of the prodrug-activating capacity of these immuno-enzymosomes by increasing the enzyme density on the immunoliposomal surface. METHODS. To achieve coupling of GUS to the **liposomes**, introduction of extra **thiol** groups was required. Two thiolating agents were examined: iminothiolane and SATA. RESULTS. When iminothiolane was used, aggregation of enzymosomes was observed above enzyme densities of 10 micrograms GUS/mumol lipid (TL). An increased electrostatic repulsion of the enzymosomes, created by inclusion of additional negatively charged lipids and by lowering the ionic strength of the external aqueous medium resulted in enzyme densities > or = 20 micrograms GUS/mumol TL without aggregation. Utilizing SATA, > or = 30 micrograms GUS/mumol TL could be **coupled** without aggregation, even at physiological ionic strength. It was shown that the enzyme density on immuno-enzymosomes, and thus on the tumor cell surface, strongly influences the antitumor effect of the prodrug daunorubicin-glucuronide against in vitro cultured ovarian cancer cells. The antitumor effect of immuno-enzymosomes with enzyme densities of about 20 micrograms GUS/mumol TL was similar to that of the parent drug daunorubicin. CONCLUSIONS. SATA-mediated thiolation of GUS-molecules enabled the preparation of immuno-enzymosomes with high enzyme densities while avoiding spontaneous aggregation. In vitro antitumor activity experiments showed that the improved immuno-enzymosome system is able to completely convert the prodrug daunorubicin-glucuronide into its parent compound.

5/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09503126 96087056 PMID: 7488618
Attachment of antibodies to sterically stabilized **liposomes**: evaluation, comparison and optimization of coupling procedures.
Hansen CB; Kao GY; Moase EH; Zalipsky S; Allen TM
Department of Pharmacology, University of Alberta, Edmonton, Canada.
Biochimica et biophysica acta (NETHERLANDS) Nov 1 **1995**, 1239 (2) p133-44, ISSN 0006-3002 Journal Code: A0W
Languages: ENGLISH
Document type: Journal Article

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         (c) 2001 BIOSIS

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Processing
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? s s2 and anthracyclin?

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           12470  ANTHRACYCLIN?
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 3/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09515617   96267507   PMID: 8710754
  Immunoliposomes     as     enzyme-carriers     (immuno-enzymosomes)     for
antibody-directed  enzyme  prodrug therapy (ADEPT): optimization of prodrug
activating capacity.
  Vingerhoeds MH; Haisma HJ; Belliot SO; Smit RH; Crommelin DJ; Storm G
  Department  of  Pharmaceutics, Faculty of Pharmacy, Utrecht Institute for
Pharmaceutical Sciences (UIPS), Utrecht University, The Netherlands.
  Pharmaceutical   research (UNITED   STATES)   Apr   1996,   13   (4)
 p604-10,  ISSN 0724-8741   Journal Code: PHS
  Languages: ENGLISH
  Document type: Journal Article
  Record type: Completed
  PURPOSE.  Immuno-enzymosomes  are  tumor-specific immunoliposomes bearing
enzymes   on   their   surface.   These   enzymes   are   capable   of   converting
relatively  nontoxic  prodrugs  into  active  cytostatic agents. The enzyme
beta-glucuronidase   (GUS)4   was   coupled   to   the   external   surface   of
immunoliposomes  directed against ovarian carcinoma cells. This study aimed
at    optimization    of    the    prodrug-activating    capacity    of    these
immuno-enzymosomes  by increasing the enzyme density on the immunoliposomal
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5/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09498222 95322531 PMID: 7599262
Poly(ethylene glycol)-modified phospholipids prevent aggregation during covalent conjugation of proteins to **liposomes**.
Harasym TO; Tardi P; Longman SA; Ansell SM; Bally MB; Cullis PR; Choi LS
University of British Columbia, Biochemistry Department, Vancouver, Canada.
Bioconjugate chemistry (UNITED STATES) Mar-Apr **1995**, 6 (2) p187-94, ISSN 1043-1802 Journal Code: A1T
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Liposome aggregation is a major problem associated with the covalent attachment of proteins to **liposomes**. This report describes a procedure for coupling proteins to **liposomes** that results in little or no change in **liposome** size. This is achieved by incorporating appropriate levels of poly(ethylene glycol)-modified lipids into the **liposomes**. The studies employed thiolated **avidin**-D **coupled** to **liposomes** containing the thio-reactive lipid N-(4-(p-maleimidophenyl)butyryl)dipalmitoyl phosphatidylethanolamine (1 mol % of total lipid) and various amounts of MePEG-S-POPE (monomethoxypoly(ethylene glycol) linked to phosphatidylethanolamine via a succinate linkage). The influence of PEG chain length and density was also assessed. The presence of PEG on the surface of **liposomes** is shown to provide an effective method of inhibiting aggregation and the corresponding increase in **liposome** size during the covalent coupling of **avidin** -D. A balance between the size of the PEG used and the amount of PEG-lipid incorporated into the **liposome** had to be achieved in order to maintain efficient coupling. Optimal coupling efficiencies in combination with minimal aggregation effects were achieved using 2 mol % MePEG2000-S-POPE (PEG of 2000 MW) or 0.8 mol % MePEG5000-S-POPE (PEG of 5000 MW). At these levels, the presence of PEG did not affect the **biotin** binding activity of the covalently attached **avidin**. The ability of the resulting **liposomes** to specifically target to biotinylated cells is demonstrated.

5/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08065543 90361937 PMID: 2391438
Optimized procedures for the coupling of proteins to **liposomes**.
Loughrey HC; Choi LS; Cullis PR; Bally MB
University of British Columbia, Faculty of Medicine, Department of Biochemistry, Vancouver, Canada.
Journal of immunological methods (NETHERLANDS) Aug 28 **1990**, 132 (1) p25-35, ISSN 0022-1759 Journal Code: IFE
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
A general, optimized method for coupling proteins to **liposomes** is presented. This procedure utilizes streptavidin covalently **coupled** to **liposomes** to allow the subsequent attachment of a variety of biotinated proteins of interest. In the first part of this study, covalent methods for coupling proteins to **liposomes** which contain the lipid derivatives MPB-PE and PDP-PE were examined. The maleimide lipid derivative MPB-PE was found to allow more efficient coupling. Thin layer chromatography however revealed that during the standard synthesis of MPB-PE, an impurity was generated which can constitute 40% or more of the derivatized PE. An improved method for the synthesis and isolation of pure MPB-PE is presented here. Subsequently, optimized conditions for the

covalent coupling of streptavidin to **liposomes** containing pure MPB-PE were determined. The flexibility of the streptavidin-**liposome** system for the preparation of various types of ligand bearing **liposomes** is demonstrated by the rapid association of a variety of biotinated proteins to streptavidin-**liposome** systems. The ability of these conjugates to target to specific cell populations in vitro as directed by defined biotinated monoclonal antibodies is demonstrated.

5/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07710727 92371778 PMID: 1324202
Free radical generation and **coupled thiol** oxidation by lactoperoxidase/SCN-/H2O2.
Lovaas E
Department of Plant Physiology and Microbiology, (IBG), University of Tromso, Norway.
Free radical biology & medicine (UNITED STATES) Sep **1992**, 13 (3) p187-95, ISSN 0891-5849 Journal Code: FRE
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The lactoperoxidase-catalyzed oxidation of glutathione (GSH) and thiocyanate (SCN-) was studied. Oxidation of SCN- was recorded by ultraviolet spectroscopy and by electron spin resonance (ESR). Consumption of GSH was measured by amperometric titration. One or two moles of GSH was oxidized per mole of H2O2 added, depending on the reaction conditions. Omission of SCN- prevented the oxidation of GSH. The oxidation of GSH required only catalytic amounts of SCN-, which was therefore recycled. Iodide (I-) could replace SCN-, while chloride or bromide were ineffective. The apparent Michaelis constant for SCN- was 17 microM. Oxidation of SCN- gave rise to two reactive intermediates, one stable and one unstable. The stable intermediate (-OSC. = N-(?)) decayed by a second-order reaction with a rate constant of 1.1 M-1 s-1. The decay of the unstable radical was very fast. The data (a) explain the short- and long-term antibacterial effects of lactoperoxidase-halide-H2O2 system, (b) point to possible deleterious effects due to glutathione depletion, (c) are of relevance for free radical diseases involving sulphur-centered free radicals, and (d) support previous observations on lipid peroxidation/halogenation in biological membranes, **liposomes**, and unsaturated fatty acids.

5/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07186563 93187376 PMID: 8445242
Liposome immunoassay (LIA) with antigen-**coupled liposomes** containing alkaline phosphatase.
Kim CK; Lim SJ
College of Pharmacy, Seoul National University, San 56-1, Shinlim-dong, Kwanak-gu, Seoul 151-742, South Korea.
Journal of immunological methods (NETHERLANDS) Feb 26 **1993**, 159 (1-2) p101-6, ISSN 0022-1759 Journal Code: IFE
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Immunoliposomes were prepared and their immunoassay applications investigated. **Liposomes** were prepared from cholesterol and phospholipids including maleimidobenzoylphosphatidylethanolamine (MBPE) for conjunction with **thiol** -containing antigens. Alkaline phosphatase (APase) was entrapped in the **liposome** and BSA, the antigen, was modified by reaction with 3-(2-pyridyl-dithio)propionyl N-hydroxysuccinimide ester (SPDP) to introduce **thiol** groups for efficient coupling. BSA-**coupled liposomes** (immunoliposomes) were incubated with

anti-BSA serum, complement, and then with APase substrate. The amount of **coupled** BSA was affected by the reaction time, the composition of the **liposome** and the BSA concentration in the reactant. The amount of enzyme released from immunoliposomes as a final result of the immunoreaction increased with increasing concentrations of complement and antibody. The **liposome** immunoassay offers a relatively rapid and simple testing procedure to quantitatively or qualitatively determine the presence or absence of antibodies, or antigenic materials for diagnostic purposes.

5/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07181582 93041887 PMID: 1384709
Development of a procedure for coupling the homing device glu-plasminogen to **liposomes**.
Heeremans JL; Kraaijenga JJ; Los P; Kluft C; Crommelin DJ
Department of Pharmaceutics, University of Utrecht, The Netherlands.
Biochimica et biophysica acta (NETHERLANDS) Oct 27 **1992**, 1117 (3) p258-64, ISSN 0006-3002 Journal Code: A0W
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The aim of this study was to find a suitable way of coupling the homing-device glu-plasminogen to the outside of **liposomes** . The described procedure is based on the reaction of **thiol** -groups introduced in the protein with **thiol**-reactive groups of the **liposome** . Details on the thiolation of proteins with the reagent succinimidyl-S-acetylthioacetate (SATA) were studied for a model-protein, amylase. Increasing the incubation-ratio SATA: amylase resulted in a gradually growing number of introduced **thiol**-groups, until a maximum of about 5 mol SH per mol amylase was reached. The enzymatic activity of the derivatized protein was even higher than that of native amylase. The **thiol** -introduction was then applied to glu-plasminogen itself. After activation with SATA, the protein was incubated with **liposomes** containing the **thiol**-reactive anchor maleimido-4-(p-phenylbutyrate)-phosphatidylethanolamine (MPB-PE). Under the chosen conditions, incubation of 0.5-2.5 mg/ml protein with 6.0-7.5 mumol/ml phospholipid for 30-120 min resulted in coupling-ratios of 20 to 94 micrograms glu-plasminogen per mumol phospholipid. This corresponds with about 140 to 660 protein molecules per **liposome** . SATA-derivatization of glu-plasminogen brought about a loss of its enzymatic activity induced by streptokinase. This activity of **liposomally coupled** plasminogen was about 52 to 74% of the activity of native glu-plasminogen (depending on the coupling-ratio). Although this may seem a significant loss of activity, it was shown that the capacity of **liposomal** glu-plasminogen to bind to its target, fibrin, was not reduced but several fold higher under the used conditions than that of the free protein. Therefore, the described method for **thiol** -introduction is an effective way to thiolate amylase without loss of activity, and to bind the homing-device glu-plasminogen to **liposomes** without substantially interfering with its fibrin-binding/homing capacity.

5/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07138349 93285194 PMID: 7685284
Our approach towards developing a specific tumour-targeted MRI contrast agent for the brain.
Go KG; Bulte JW; de Ley L; The TH; Kamman RL; Hulstaert CE; Blaauw EH; Ma LD
Department of Neurosurgery, University Hospital Groningen, Netherlands.
European journal of radiology (NETHERLANDS) Apr **1993**, 16 (3)

p171-5, ISSN 0720-048X Journal Code: EM6
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

This review presents various aspects of the technological development, and their assessment in the design of a contrast agent for MRI, tailored to visualise tumours in the brain. First, it was demonstrated that magnetite as a contrast agent exhibited a much stronger relaxivity than gadolinium. The prepared magnetite particles bound to dextran, were also shown to be of appropriate size by electron microscopy. After their intravenous injection into rats with blood-brain barrier disruption, the lesion was strongly enhanced by T2-shortening. Furthermore, monoclonal antibodies directed against small cell lung carcinoma, proved to be able to penetrate into tumours, which had been raised by implantation of the small cell lung carcinoma cells into the brains of nude rats. As to the essential step, it was demonstrated in vitro that magnetite particles **coupled** to monoclonal antibodies by the **biotin**-streptavidin binding, could be bound to the target cells of the antibody, changing the relaxation rates of the latter. Finally it could be shown in vitro that an alternative approach, using lymphocytes to be targeted to tumour cells, also proved feasible, in that these lymphocytes could be labelled with magnetite that had been incorporated into **liposomes**. Further developments will be the in vivo assessment of the acquired progress in experimental animals, before clinical application is warranted.

5/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06610844 88299100 PMID: 3403675
Chromatography of functionalized **liposomes** and their components.
Schott H; Leitner B; Schwendener RA; Hengartner H
Institut fur Organische Chemie, Universitat Tubingen, F.R.G.
Journal of chromatography (NETHERLANDS) May 27 **1988**, 441 (1)
p115-24, ISSN 0021-9673 Journal Code: HQF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The antitumour drug 1-beta-D-arabinofuranosylcytosine (ara C) was acylated by means of oleic acid anhydride, resulting in the prodrug N4-oleoyl-ara C. Together with a lipophilic **biotin** derivative, this lipophilic prodrug was incorporated into the bilayer membrane of unilamellar **liposomes** prepared by means of the detergent dialysis method. On addition of these biotinylated prodrug-**liposomes** to an excess of **avidin**, **biotin** residues were complexed with **avidin**. The unreacted **avidin** was removed by chromatography on the Ultrogel AcA-22 column. The prodrug-**liposome-avidin** complex was **coupled** to biotinylated monoclonal antibodies through the free binding sites of the immobilized **avidin**. Unreacted antibodies were removed by chromatography on an Ultrogel AcA-22 column. In vitro, the **liposome** -antibody complexes selectively bound to cells which were recognized by the monoclonal antibodies linked to the **liposomes**. For this reason, a promising strategy towards a specific chemotherapy of cancer is expected.

5/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06056321 86313626 PMID: 3462715
Carrier-directed targeting of **liposomes** and erythrocytes to denuded areas of vessel wall.
Smirnov VN; Domogatsky SP; Dolgov VV; Hvatov VB; Klibanov AL; Koteliansky VE; Muzykantov VR; Repin VS; Samokhin GP; Shekhonin BV; et al
Proceedings of the National Academy of Sciences of the United States of

America (UNITED STATES) Sep **1986**, 83 (17) p6603-7, ISSN 0027-8424 Journal Code: V3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Immunomorphological staining of specimens prepared from human carotid arteries with anti-collagen type I antibodies reveals large amounts of type I collagen in the subendothelium of lipid fibrous plaques. Collagen type I-containing structures, once in direct contact with blood after plaque rupture, can serve as potential targets for selective delivery of **liposomes** and erythrocytes to these areas. To verify this rationale, [14C]cholesterol oleate-containing **liposomes** were conjugated with bovine or human anti-collagen type I antibodies or human plasma fibronectin. **Biotin** derivatives of human anti-collagen type I antibody were **coupled** to human erythrocytes. Modified **liposomes** and erythrocytes were perfused in situ through segments of bovine, rabbit, or human arteries partially denuded with a balloon catheter prior to perfusion. After perfusion, the control and denuded areas were excised and subjected to scanning electron microscopic analysis and measurements of associated radioactivity. It was found that conjugates of **liposomes** or erythrocytes with anti-collagen type I antibodies or fibronectin are selectively bound by endothelium-free zones of arterial segments. Carrier-directed targeting of drug-laden **liposomes** and erythrocytes to thrombosis-prone areas of arterial lumen is discussed.

5/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06045788 85305739 PMID: 2864019
Differential effects of triphenyltin and 8-azido-ATP on the ATP synthesis, ATP-Pi exchange, and ATP hydrolysis in **liposomes** containing ATP synthase and bacteriorhodopsin.
Van der Bend RL; Duetz W; Colen AM; Van Dam K; Berden JA
Archives of biochemistry and biophysics (UNITED STATES) Sep **1985**, 241 (2) p461-71, ISSN 0003-9861 Journal Code: 6SK
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The ATP hydrolysis activity of purified ATP synthase reconstituted in **liposomes** was inhibited by triphenyltin in a manner different from that of other **thiol**-specific reagents. In **liposomes** containing ATP synthase and bacteriorhodopsin, ATP hydrolysis and ATP-Pi exchange were inhibited by triphenyltin to a greater extent than the ATP synthesis, in contrast to what was found with an F1-specific inhibitor, 8-azido-ATP. The possibility is discussed that ATP hydrolysis and ATP synthesis are differently **coupled** to proton conduction through F0.

5/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04924683 84283275 PMID: 6467563
Highly sensitive immunoassays based on use of **liposomes** without complement.
Litchfield WJ; Freytag JW; Adamich M
Clinical chemistry (UNITED STATES) Sep **1984**, 30 (9) p1441-5, ISSN 0009-9147 Journal Code: DBZ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We describe a novel **liposome**-based immunoassay in which covalently linked hapten-cytolysin conjugates are used instead of complement and surface-immobilized immunoreagents. Stable, unilamellar **liposomes** containing entrapped alkaline phosphatase as a marker enzyme were prepared

by dialysis of octyl glucoside from suspensions of cholesterol and egg yolk lecithin. The resulting vesicles could be immediately lysed by addition of either bee venom melittin or hapten-melittin conjugates. Using ouabain, an analog of digoxin, we synthesized conjugates that were more lytic than mellitin alone but that were inhibited in the presence of antibody. This inhibition was affected by adding competing free digoxin at various concentrations to obtain standard curves. The same **liposome** preparations could be lysed with a **biotin**-melittin conjugate, which was inhibited by **avidin**. The latter system was affected by free **biotin** and might be used to **couple** this approach to various heterogeneous immunoassays.

5/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04136077 84158011 PMID: 6561136
Immunospecific vesicle targeting facilitates fusion with selected cell populations.
Guyden J; Godfrey W; Doe B; Ousley F; Wofsy L
Ciba Foundation symposium (NETHERLANDS) **1984**, 103 p239-53, ISSN 0300-5208 Journal Code: D7X
Contract/Grant No.: CA-24436, CA, NCI; CA-9179, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Antibody-directed targeting of vesicles to cells dramatically enhances polyethylene glycol-mediated fusion and microinjection. Sealed erythrocyte ghosts or **liposomes**, containing fluorescent bovine serum albumin, were targeted to murine spleen and thymus cells, and to lymphocyte and monocyte cell lines. In all cases, targeted cell populations showed substantial levels of microinjection, whereas populations treated with the fusogen in the absence of targeting were not significantly microinjected. Attachment of vesicles to selected cells was achieved by first labelling the cells with **biotin**-modified antibody and then treating them with **avidin-coupled** sealed ghosts or **liposomes**. Another approach to the promotion of selective fusion aims to alter the cell recognition properties of Sendai virus so that its fusogenic activity may be redirected to specific cellular targets. The agglutination and fusion of red cells by UV-inactivated Sendai virus were completely blocked by low concentrations of a Fab preparation of a monoclonal antibody against the viral haemagglutinin (HN) sites. Agglutination and fusion activity were restored in the presence of Fab-anti-HN by providing an alternative recognition system, namely, when the virus had been **coupled** with **biotin** and the red cells with **avidin**. Methods for facilitating microinjection by specifically directing vesicles to target cells may be particularly useful in overcoming barriers to the transfer of genes into lymphocytes by standard transfection techniques.

5/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04131108 83289419 PMID: 6193054
Immune response mediated by **liposome**-associated protein antigens. III. Immunogenicity of bovine serum albumin covalently **coupled** to vesicle surface.
Shek PN; Heath TD
Immunology (ENGLAND) Sep **1983**, 50 (1) p101-6, ISSN 0019-2805 Journal Code: GH7
Contract/Grant No.: CA 25526, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
A protein antigen, bovine serum albumin (BSA), was covalently linked to

the surface of preformed large unilamellar vesicles composed of phosphatidylcholine, cholesterol, and N-[4-(p-maleimidophenyl)butyryl]phosphatidylethanolamine (MPB-PE). The interaction between thiolated BSA and MPB-PE resulted in the production of a protein-**liposome** conjugate via the formation of an irreversible covalent bond. Mice immunized with **liposome-coupled** BSA were found to generate a vigorous BSA-specific plaque-forming cell (PFC) response. No significant response was observed in control animals given simultaneous, but separate injections of **thiol**-BSA and **liposomes**. Thus, there seems to be a need for successful and stable linkage between the antigen and the carrier. The elicitation of an optimal antigen-specific PFC response was also found to require the vesicle surface to be coated with a certain minimum distribution of the antigen. Results of this study demonstrate that the covalent coupling of a protein antigen to the **liposome** surface is very effective in potentiating the protein-specific antibody response and the immunogenicity of the conjugate is dependent on the epitope density of the antigen.

5/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04120686 82167591 PMID: 6896053
Plasma protein-facilitated **coupled** exchange of phosphatidylcholine and cholesteryl ester in the absence of cholesterol esterification.
Ihm J; Ellsworth JL; Chataing B; Harmony JA
Journal of biological chemistry (UNITED STATES) May 10 **1982**, 257 (9) p4818-27, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: GM 19631, GM, NIGMS; HL 07382, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

A protein(s) which catalyzes the exchange of phosphatidylcholine and cholesteryl ester between plasma lipoproteins has been purified 10,000-fold from lipoprotein-free human plasma. The apparent molecular weight of the protein of the active fraction, designated lipid transfer complex (LTC), is approximately 61,000; when electrophoresed in 6 M urea, 0.1% sodium dodecyl sulfate on a 3-20% polyacrylamide gradient, the protein appears as a doublet of molecular weights 58,000 and 63,000. The active material is a glycoprotein which binds to concanavalin A. Human LTC is a lipid-protein complex with phospholipid, cholesterol, cholesteryl ester, and glyceride comprising 7% of the total mass. A similar glycoprotein (or glycoproteins) exists in rat plasma, although the fold-purification thus far achieved is low: about 500-fold. Moreover, the rat preparation enhances exchange of phosphatidylcholine, but does not appreciably enhance exchange of cholesteryl ester. Partially purified LTC (less than or equal to 3500-fold) exists in a complex with lecithin: cholesterol acyltransferase. Active lecithin: cholesterol acyltransferase is not, however, required for exchange of phosphatidylcholine or cholesteryl ester facilitated by human LTC. The rates of exchange of phosphatidylcholine and cholesteryl ester facilitated by human LTC are equal. **Coupled** lipid exchange occurs at all stages of LTC purification, at values of pH between 5 and 10, and at ionic strengths as great as 0.9. Moreover, phosphatidylcholine and cholesteryl ester are exchanged with 1:1 stoichiometry in the presence of **thiol** group reagents such as 5,5'-dithiobis-(2-nitrobenzoic acid). Both lipid exchange activities are relatively resistant to elevated temperatures. **Coupled** exchange of phospholipid and neutral lipid is not dictated by the nature of the lipoprotein donor and acceptor substrates: bovine liver phospholipid exchange protein catalyzes exchange of phosphatidylcholine but not cholesteryl ester between low and high density lipoproteins under conditions identical with those in which human LTC facilitates exchange of both lipids.

5/3,AB/20 (Item 20 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

04117072 82023969 PMID: 7284322
Immunospecific targeting of **liposomes** to cells: a novel and efficient method for covalent attachment of Fab' fragments via disulfide bonds.
Martin FJ; Hubbell WL; Papahadjopoulos D
Biochemistry (UNITED STATES) Jul 7 **1981**, 20 (14) p4229-38, ISSN 0006-2960 Journal Code: A0G
Contract/Grant No.: CA-25526, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
An efficient method for covalently cross-linking 50K Fab' antibody fragments to the surface of lipid vesicles is reported. Coupling up to 600 microgram of Fab'/mumol of phospholipid (about 6000 Fab' molecules per 0.2-micrometer vesicle) is achieved via a disulfide interchange reaction between the **thiol** group exposed on each Fab' fragment and a pyridyldithio-derivative of phosphatidylethanolamine present in low concentration in the membranes of preformed large unilamellar vesicles. The coupling reaction is efficient, proceeds rapidly under mild conditions, and yields well-defined products. Each vesicle-linked Fab' fragment retains its original antigenic specificity and full capacity to bind antigen. We have used Fab' fragments, **coupled** to vesicles by this method, to achieve immunospecific targeting of **liposomes** to cells in vitro. Vesicles bearing antihuman erythrocyte Fab' fragments bind quantitatively to human erythrocytes (at multiplicities up to 5000 0.2-micrometer vesicles per cell) while essentially no binding is observed to sheep or ox red blood cells. Vesicle-cell binding is stable over a pH range from 6 to 8 and is virtually unaffected by the presence of human serum (50%). Cell-bound vesicles retain their aqueous contents and can be eluted intact from cells by treatment with reducing agents (dithiothreitol or mercaptoethanol) at alkaline pH.

5/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

03530621 79124759 PMID: 420828
On the mode of **liposome**-cell interactions. **Biotin**-conjugated lipids as ultrastructural probes.
Bayer EA; Rivnay B; Skutelsky E
Biochimica et biophysica acta (NETHERLANDS) Feb 2 **1979**, 550 (3) p464-73, ISSN 0006-3002 Journal Code: A0W
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
An efficient method for labeling and visualizing phospholipids at the ultrastructural level is described. **Biotin** was **coupled** to the amines of appropriate phospholipids via the N-hydroxysuccinimide ester. The biotinylated lipid could be specifically labeled by ferritin-**avidin** conjugates and detected by transmission electron microscopy. The lipid derivatives were analyzed and evaluated in terms of their resemblance to the original lipid. Although differing in some aspects from the parent lipid molecules, the biotinyl derivatives still retain the basic characteristics of lipids vis-a-vis their orientation and position in the membrane bilayer. The latter property renders the biotinylated lipid qualitatively suitable for tracing the fate of the lipid component(s) of **liposomes** during their interaction with biological membranes of various cell types. Using this system, we propose that the extent and pattern of the **liposome**-cell interaction depends, at least in part, on the cell type employed. This observation may be due to intrinsic variations in cell surface structure and properties relative to those of the **liposome**.

11810700 BIOSIS NO.: 199900056809
Energy coupling and ATP synthase.
AUTHOR: Haraux Francis(a); De Kouchkovsky Yaroslav
AUTHOR ADDRESS: (a)Sect. Bioenergetique, CEA Saclay, F-91191 Gif-sur-Yvette **France
JOURNAL: Photosynthesis Research 57 (3):p231-251 Sept., **1998**
ISSN: 0166-8595
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This review is focused on the chloroplast (i.e. thylakoid) ATP synthase-hydrolase (ATPase) but also refers to the bacterial and mitochondrial cases when relevant. (1) A proton-translocating F-ATPase (CF-ATPase in chloroplasts) comprises an intramembrane proton channel, F0, and an extramembrane catalytic head, F1, the latter forming a 'ball' of 3 alternative **couples** of alpha and beta subunits plus one copy of each gamma, delta, epsilon subunit; alpha and beta subunits bear regulatory and catalytic nucleotide binding sites, respectively. F0 acts as a motor, with a stator made of subunits IV (a in prokaryotes), I and II (b, b'), and a rotor arranged in a crown of 9-12 subunits III (c). Subunit gamma, anchored to the rotor, thus turns with the latter while its other extremity, entering into F1, induces periodical conformational changes that allow binding of substrates on one beta and release of products from another. The energy is supplied by the proton gradient built by the redox chain. Thus, one H+ from the high potential compartment (thylakoid lumen) protonates, via part of subunit a, a neighboring subunit c while another c nearby, facing the other part of a, is deprotonated and the resulting H+ escapes into the low potential compartment (chloroplast stroma). (2) The mechanistic stoichiometry H+/ATP of protons transported per ATP formed was initially found to equal 2-3 but is now considered to equal 4. Such a shift may be due to the diversity of material (chloroplasts, mitochondria, bacteria, **liposomes**), techniques (steady-state vs. pH or salt jumps) and approaches (kinetic: 'flow-flow', or thermodynamic: 'force-force' methods). In mitochondria, after subtraction of the H+ due to Pi translocation, H+/ATP is close to 3, perhaps due to a smaller number of c subunits (H+/ATP = c/beta). (3) The osmotic (DELTApH) and electric (DELTApsi) components of total DELTAmuH+ are thermodynamically interconvertible and, despite some conflicting results, also seem kinetically equivalent. This is thanks to a 'proton well', a scheme of which is presented. A related problem is whether phosphorylation depends on pHin and pHout or solely on their difference (= DELTApH). No consensus exists on how the enzyme affinity for ADP, expressed by its Km, may depend on DELTAmuH+. Two models are discussed. One is the simultaneous binding of an ADP and release of an ATP, driven by the simultaneous translocation of 4 protons while the other introduces an intermediary step. (4) Besides being an energetic source for ATP synthesis, DELTAmuH+ switches ATPase from inactive to active state and, specifically for CF1, exposes a disulfide bridge of gamma to **thiol**-reducing agents, thioredoxin in vivo (reduced by Photosystem I), DTT in vitro. This reduction lowers the activation for threshold DELTAmuH+ and at the same time prolongs the life-time of the active enzyme from milliseconds to minutes after dissipation of DELTAmuH+. By using ATPase inhibitors before or after activation, we have suggested that activating and catalytic protons are different (actually, activation does not necessarily require a proton flow). Activation is also accompanied - or governed - by conformational changes. In mitochondria, there is an unbinding of a special subunit IF1 from F1; its equivalent for CF1 could be a conformational change of epsilon. A final remark concerns the

physiological role of (de)activation, if any. It was proposed that inactive state of CF c[redacted]d prevent futile hydrolysis of [redacted]P in dark, but in fact, thanks to the low DELTAmuH+ threshold required for activation of reduced CF1 and to low membrane permeability to protons in vivo, a minute consumption of ATP is sufficient to maintain a high enough DELTAmuH+ to oppose a counter-protonmotive force limiting sustained ATP hydrolysis.

1998

5/3,AB/23 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08401515 BIOSIS NO.: 000094119169
FREE RADICAL GENERATION AND **COUPLED THIOL** OXIDATION BY LACTOPEROXIDASE-THIOCYANATE-HYDROGEN PEROXIDE
AUTHOR: LOVAAS E
AUTHOR ADDRESS: BIO-SEA, MARIELUND 7, N-9000 TROMSO, NORWAY.
JOURNAL: FREE RADICAL BIOL MED 13 (3). 1992. 187-195. **1992**
FULL JOURNAL NAME: Free Radical Biology & Medicine
CODEN: FRBME
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The lactoperoxidase-catalyzed oxidation of glutathione (GSH) and thiocyanate (SCN-) was studied. Oxidation of SCN- was recorded by ultraviolet spectroscopy and by electron spin resonance (ESR). Consumption of GSH was measured by amperometric titration. One or two moles of GSH was oxidized per mole of H2O2 added, depending on the reaction conditions. Omission of SCN- prevented the oxidation of GSH. The oxidation of GSH required only catalytic amounts of SCN-, which was therefore recycled. Iodide (I-) could replace SCN-, while chloride or bromide were ineffective. The apparent Michaelis constant for SCN- was 17 .mu.M. Oxidation of SCN- gave rise to two reactive intermediates, one stable and one unstable. The stable intermediate (-OSC..dbd.N-(?)) decayed by a second-order reaction with a rate constant of 1.1 M-1 s-1. The decay of the unstable radical was very fast. The data (a) explain the short- and long-term antibacterial effects of lactoperoxidase-halide-H2O2 system, (b) point to possible deleterious effects due to glutathione depletion, (c) are of relevance for free radical diseases involving sulphur-centered free radicals, and (d) support previous observations on lipid peroxidation/halogenation in biological membranes, **liposomes**, and unsaturated fatty acids.

1992

5/3,AB/24 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06929116 BIOSIS NO.: 000089062510
LIPOPHILIC DISULFIDE PRODRUGS SYNTHESES AND DISULFIDE BOND CLEAVAGE
AUTHOR: MUELLER C E; DANIEL P T; HOLZSCHUH J; ROTH H J
AUTHOR ADDRESS: PHARMAZEUTISCHES INST., UNIV. TUEBINGEN, AUF DER MORGENSTELLE 8, D-7400 TUEBINGEN, FRG.
JOURNAL: INT J PHARM (AMST) 57 (1). 1989. 41-48. **1989**
FULL JOURNAL NAME: International Journal of Pharmaceutics (Amsterdam)
CODEN: IJPHD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Various drugs bearing a **thiol** or thione function were **coupled** with activated lipophilic **thiol** derivatives to afford

unsymmetrical disulfides. Synthetic methods were developed to introduce one or two long alkyl chains into drug molecules in order to obtain highly lipophilic prodrugs. These might be suitable to form bilayers or for integration into **liposomes**. Disulfide bond cleavage was assessed by preincubation of the 6-MP prodrug 2 in serum followed by a bioassay. The preincubation period did not increase the inhibitory potency of the prodrug on lymphocyte proliferation as compared to the parent drug. The disulfide bond cleavage of prodrug 2 is assumed to be an active cellular process.

1989

5/3,AB/25 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05054940 BIOSIS NO.: 000081013064
DIFFERENTIAL EFFECTS OF TRIPHENYLTIN AND 8 AZIDO-ATP ON THE ATP SYNTHESIS ATP INORGANIC PHOSPHATE EXCHANGE AND ATP HYDROLYSIS IN **LIPOSOMES** CONTAINING ATP SYNTHASE AND BACTERIORHODOPSIN
AUTHOR: VAN DER BEND R L; DUETZ W; COLEN A-M A F; VAN DAM K; BERDEN J A
AUTHOR ADDRESS: LAB. BIOCHEM., B. C. P. JANSEN INST., UNIV. AMST., P.O. BOX 20151, 1000 HD AMSTERDAM, NETH.
JOURNAL: ARCH BIOCHEM BIOPHYS 241 (2). 1985. 461-471. **1985**
FULL JOURNAL NAME: Archives of Biochemistry and Biophysics
CODEN: ABBIA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The ATP hydrolysis activity of purified ATP synthase reconstituted in **liposomes** was inhibited by triphenyltin in a manner different from that of other **thiol**-specific reagents. In **liposomes** containing ATP synthase and bacteriorhodopsin, ATP hydrolysis and ATP-Pi exchange were inhibited by triphenyltin to a greater extent than the ATP synthesis, in contrast to what was found with an F1-specific inhibitor, 8-azido-ATP. The possibility is discussed that ATP hydrolysis and ATP synthesis are differently **coupled** to proton conduction through F0.

1985

5/3,AB/26 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03556361 BIOSIS NO.: 000073059442
AFFINITY TARGETING OF MEMBRANE VESICLES TO CELL SURFACES
AUTHOR: GODFREY W; DOE B; WALLACE E F; BREDT B; WOFSY L
AUTHOR ADDRESS: DEP. MICROBIOL., IMMUNOL., UNIV. CALIFORNIA, BERKELEY, CALIF. 94720, USA.
JOURNAL: EXP CELL RES 135 (1). 1981. 137-146. **1981**
FULL JOURNAL NAME: Experimental Cell Research
CODEN: ECREA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: A general methodology was developed for immunospecific attachment of sealed erythrocyte ghosts or **liposomes** to selected cell surface antigens. Antibody or **avidin** is **coupled** to a red cell or **liposome** membrane by 1 of several simple chemical procedures. Membrane vesicles bearing anti-hapten antibody or **avidin** form clusters exclusively around cells that were labeled with 1st-layer hapten- or **biotin**-modified antibodies. Such targeting methods

should be useful in studies aimed at facilitating vesicle-cell fusion and microinjection of selected molecules into cells. The new protein-membrane coupling procedures are also readily applied to the preparation of selectively modified red cells for use in plaque assays to detect cells secreting immunoglobulin or a specific anti-protein antibody.

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? s glycoprotein? and (alpha or alpha (w) 1)

Processing
          240684  GLYCOPROTEIN?
         1109033  ALPHA
         1109033  ALPHA
         6301851  1
           92110  ALPHA(W)1
      S1   37199  GLYCOPROTEIN? AND (ALPHA OR ALPHA (W) 1)
? s doxorubicin?

      S2   65301  DOXORUBICIN?
? s s1 or s2

           37199  S1
           65301  S2
      S3  102168  S1 OR S2
? s s3 and tumor? and treat?

          102168  S3
         1377188  TUMOR?
         3784730  TREAT?
      S4   15964  S3 AND TUMOR? AND TREAT?
? s s4 and desialyat?

           15964  S4
              61  DESIALYAT?
      S5       0  S4 AND DESIALYAT?
? s s4 and asialoglycoprotein?

           15964  S4
            3338  ASIALOGLYCOPROTEIN?
      S6       7  S4 AND ASIALOGLYCOPROTEIN?
? rd

...completed examining records
      S7       7  RD (unique items)
? t s7/3,ab/all


7/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11481094   21361118   PMID: 11467948
    Glycoengineering of therapeutic glycoproteins : in vitro
galactosylation and sialylation of glycoproteins with terminal
n-acetylglucosamine and galactose residues.
  Raju TS; Briggs JB; Chamow SM; Winkler ME; Jones AJ
  Analytical Chemistry, Genentech Inc., One DNA Way, South San Francisco,
California 94080.
  Biochemistry (United States) Jul 31 2001, 40 (30) p8868-76, ISSN
0006-2960 Journal Code: A0G
  Languages: ENGLISH
  Document type: Journal Article
  Record type: In Process
  Therapeutic glycoproteins produced in different host cells by
recombinant DNA technology often contain terminal GlcNAc and Gal residues.
Such glycoproteins clear rapidly from the serum as a consequence of
binding to the mannose receptor and/or the asialoglycoprotein
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receptor in the liver. To increase the serum half-life of these **glycoproteins**, we carried out in vitro glycosylation experiments using TNFR-IgG, an immunoadhesin molecule, as a model therapeutic **glycoprotein**. TNFR-IgG is a disulfide-linked dimer of a polypeptide composed of the extracellular portion of the human type 1 (p55) **tumor** necrosis factor receptor (TNFR) fused to the hinge and Fc regions of the human IgG(1) heavy chain. This bivalent antibody-like molecule contains four N-glycosylation sites per polypeptide, three in the receptor portion and one in the Fc. The heterogeneous N-linked oligosaccharides of TNFR-IgG contain sialic acid (Sia), Gal, and GlcNAc as terminal sugar residues. To increase the level of terminal sialylation, we regalactosylated and/or resialylated TNFR-IgG using beta-1,4-galactosyltransferase (beta1,4GT) and/or **alpha**-2,3-sialyltransferase (alpha2,3ST). **Treatment** of TNFR-IgG with beta1,4GT and UDP-Gal, in the presence of MnCl(2), followed by MALDI-TOF-MS analysis of PNGase F-released N-glycans showed that the number of oligosaccharides with terminal GlcNAc residues was significantly decreased with a concomitant increase in the number of terminal Gal residues. Similar **treatment** of TNFR-IgG with alpha2,3ST and CMP-sialic acid (CMP-Sia), in the presence of MnCl(2), produced a molecule with an approximately 11% increase in the level of terminal sialylation but still contained oligosaccharides with terminal GlcNAc residues. When TNFR-IgG was **treated** with a combination of beta1,4GT and alpha2,3ST (either in a single step or in a stepwise fashion), the level of terminal sialylation was increased by approximately 20-23%. These results suggest that in vitro galactosylation and sialylation of therapeutic **glycoproteins** with terminal GlcNAc and Gal residues can be achieved in a single step, and the results are similar to those for the stepwise reaction. This type of in vitro glycosylation is applicable to other **glycoproteins** containing terminal GlcNAc and Gal residues and could prove to be useful in increasing the serum half-life of therapeutic **glycoproteins**.

7/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09578049 97447239 PMID: 9301690

Ricin fusion toxin targeted to the human granulocyte-macrophage colony stimulating factor receptor is selectively toxic to acute myeloid leukemia cells.

Burbage C; Tagge EP; Harris B; Hall P; Fu T; Willingham MC; Frankel AE
Department of Medicine, Medical University of South Carolina, Charleston, USA.

Leukemia research (ENGLAND) Jul 1997, 21 (7) p681-90, ISSN 0145-2126 Journal Code: K9M
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Treatment failure of patients with acute myelogenous leukemia (AML) is frequently due to the development of multidrug resistance phenotype blasts. We have expressed a fusion protein consisting of human granulocyte-macrophage colony stimulating factor (GMCSF) fused to the N-terminus of a lectin-deficient ricin toxin B chain (RTB) in Spodoptera frugiperda insect cells. The fusion protein was purified by immunoaffinity chromatography and reassociated with chemically deglycosylated ricin toxin A chain (RTA). The resulting fusion toxin was found to react with antibodies to GMCSF, RTB and RTA and had the predicted molecular mass of 80 kDa. GMCSF-ricin bound poorly to asialofetuin (Kd = 10(6) M-1) and receptor negative cells indicating loss of lectin activity, but bound strongly to GMCSF receptor positive HL60 cells. Ligand displacement assays showed fusion toxin affinity 2.6-fold less than native GMCSF. Selective inhibition of protein synthesis was observed on receptor positive cells. Induction of apoptosis was also observed on receptor positive cells. Cells expressing multidrug resistance gene products (P-gp, Bcl2 and BclXL) were also sensitive to fusion toxin. These results suggest that GMCSF-ricin deserves

further preclinical development.

7/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08638828 96078412 PMID: 7579799
CD23 molecule acts as a galactose-binding lectin in the cell aggregation of EBV-transformed human B-cell lines.
Kijimoto-Ochiai S; Uede T
Section of Immunopathogenesis, Hokkaido University, Sapporo, Japan.
Glycobiology (ENGLAND) Jun 1995, 5 (4) p443-8, ISSN 0959-6658 Journal Code: BEL
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Epstein-Barr virus (EBV)-transformed human B-cell lines, L-KT9 and DH3 cells express CD23 antigen, and grow in a mixture of single and aggregated cells. The CD23 molecule has high amino acid sequence homology with C-type lectin and recently we have shown that the solubilized CD23 molecule can really interact with galactose residues on **glycoproteins**. In this study, therefore, we tested whether CD23 antigen on the cell surface really acts as a galactose-binding lectin in the aggregation of these cells. The EBV-transformed cells (L-KT9) were separated into an aggregated-cell-rich fraction and a single-cell-rich fraction. Aggregated cells disaggregated after removal of galactose by beta-galactosidase **treatment**, whereas single cells made large aggregation on sialidase **treatment**, and this aggregation was inhibited in the presence of asialo-fetuin. On the other hand, naturally aggregated cells become single cells with anti-CD23 monoclonal antibody (mAB) as well as the soluble form of CD23, but not with anti-CD21 mAB. In addition, L-KT9 and DH3 cells bound to asialo-fetuin-coupled Sepharose (ASF-Sepharose) and this binding was significantly inhibited by pre-**treatment** of cells with anti-CD23, but not with anti-CD21 or other anti-adhesion molecules. From these results, we conclude that the naturally aggregated state of EBV-transformed cells occurs mainly through the interaction of CD23 as a lectin molecule and galactose residues as its ligand.

7/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05034415 86271736 PMID: 3731108
Cell surface sialomucin and resistance to natural cell-mediated cytotoxicity of rat mammary **tumor** ascites cells.
Sherblom AP; Moody CE
Cancer research (UNITED STATES) Sep 1986, 46 (9) p4543-6, ISSN 0008-5472 Journal Code: CNF
Contract/Grant No.: CA33238, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
MAT-B1 and MAT-C1 ascites sublines of the 13762 rat mammary adenocarcinoma both contain sialomucin as a major cell surface component and are resistant to cytolysis by normal rat spleen lymphocytes [3 +/- 2% (SD) and 0 +/- 1%, respectively]. Susceptibility to lysis did not increase following **treatment** of cells with neuraminidase, fucosidase, or **alpha**- or beta-galactosidase. **Treatment** with trypsin significantly increased the susceptibility of MAT-B1 (14 +/- 3%) but not MAT-C1 (5 +/- 2%). Following 1 month in culture, the sialomucin content of MAT-B1 cells dropped from 30% to 8% (determined by glucosamine labeling) and natural cell-mediated cytolysis increased to 16 +/- 4%, whereas the sialomucin content and susceptibility of MAT-C1 cells did not change. The results indicate that the relatively minor changes associated with removal of cell surface sialic acid or fucose residues do not result in increased

susceptibility of the [redacted]cites cells to cytolysis. Howe[redacted], susceptibility of MAT-B1 cells to l[redacted]s by normal rat spleen lympho[redacted]es was inversely correlated with the amount of major **glycoprotein** (r = -0.96).

7/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04727642 81243341 PMID: 6265689
[Approaches to a selective chemotherapy of hepatocellular carcinoma (author's transl)]
Ansatze zur selektiven Chemotherapie des hepatozellularen Karzinoms.
Pausch J; Holstege A; Keppler D; Gerok W
Klinische Wochenschrift (GERMANY, WEST) Jun 15 1981, 59 (12) p591-8, ISSN 0023-2173 Journal Code: KWH
Languages: GERMAN
Document type: Journal Article
Record type: Completed
1. An improvement of the chemotherapy of hepatocellular carcinoma with adriamycin or 5-fluorouracil and a reduction of side effects has been achieved by intra-arterial administration of the drugs. This **treatment** provides a somewhat extended survival but no cure. 2. The **treatment** of hepatocellular carcinoma in patients by reduction of an inactive precursor of a cytocidal alkylating agent by azoreductase of the **tumor** showed no therapeutic effect. 3. A selective hepatocellular uptake of drugs coupled to **asialoglycoproteins** has been described. An application of this concept for the chemotherapy of hepatocellular carcinoma seems doubtful since a loss of binding proteins for desialylated glycoproteins during experimental hepatocarcinogenesis has been demonstrated. 4. The increased uptake of 5-fluorouridine in hepatomas after induction of a tissue-specific depletion of uridine 5'-triphosphate and cytidine 5'-triphosphate provides an effective experimental chemotherapy with limited side effects. A clinical use of this new concept for the chemotherapy of hepatocellular carcinoma may serve as a useful approach.

7/3,AB/6 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

11258899 EMBASE No: 2001273432
Glycoengineering of therapeutic **glycoproteins**: In vitro galactosylation and sialylation of **glycoproteins** with terminal N-acetylglucosamine and galactose residues.
Shantha Raju T.; Briggs J.B.; Chamow S.M.; Winkler M.E.; Jones A.J.S.
T. Shantha Raju, Analytical Chemistry, Genentech Inc., One DNA Way, South San Francisco, CA 94080 United States
AUTHOR EMAIL: sraju@gene.com
Biochemistry (BIOCHEMISTRY) (United States) 31 JUL 2001, 40/30 (8868-8876)
CODEN: BICHA ISSN: 0006-2960
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 28

Therapeutic **glycoproteins** produced in different host cells by recombinant DNA technology often contain terminal GlcNAc and Gal residues. Such **glycoproteins** clear rapidly from the serum as a consequence of binding to the mannose receptor and/or the **asialoglycoprotein** receptor in the liver. To increase the serum half-life of these **glycoproteins**, we carried out in vitro glycosylation experiments using TNFR-IgG, an immunoadhesin molecule, as a model therapeutic **glycoprotein**. TNFR-IgG is a disulfide-linked dimer of a polypeptide composed of the extracellular portion of the human type 1 (p55) **tumor** necrosis factor receptor (TNFR) fused to the hinge and Fc regions of the

13145903 BIOSIS NO.: 200100353052
Elevation of serum asialo-alpha1 acid **glycoprotein** concentration in patients with hepatic cirrhosis and hepatocellular carcinoma as measured by antibody-lectin sandwich assay.
AUTHOR: Song E Y(a); Kim K A; Kim Y D; Lee H S(a); Kim H J; Ahn B M; Chung T W
AUTHOR ADDRESS: (a)KRIBB, Daejon**South Korea
JOURNAL: Clinical Chemistry 47 (S6):pA152 June, 2001
MEDIUM: print
CONFERENCE/MEETING: 53rd Annual Meeting of the AACC/CSCC Chicago, Illinois, USA July 29-August 02, 2001
ISSN: 0009-9147
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English

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Set     Items   Description
S1      37199   GLYCOPROTEIN? AND (ALPHA OR ALPHA (W) 1)
S2      65301   DOXORUBICIN?
S3     102168   S1 OR S2
S4      15964   S3 AND TUMOR? AND TREAT?
S5          0   S4 AND DESIALYAT?
S6          7   S4 AND ASIALOGLYCOPROTEIN?
S7          7   RD (unique items)
S8          0   S4 AND AGPR AND DOXORUBICIN?
S9         19   DESIALYATED AND GLYCOPROTEIN?
S10        16   RD (unique items)
S11         2   S10 AND TUMOR?
S12       400   S4 AND LIPOSOME?
S13       244   RD (unique items)
S14         1   S13 AND ((AVIDIN AND BIOTIN) OR (THIOL AND MALEAMIDE))
? s s4 and (vincristine or daunorubicin or antisens? or ribozym?)

          15964  S4
          49428  VINCRISTINE
          15750  DAUNORUBICIN
          41275  ANTISENS?
           7325  RIBOZYM?
     S15   4486  S4 AND (VINCRISTINE OR DAUNORUBICIN OR ANTISENS? OR
                 RIBOZYM?)
? s s15 and liposome?

           4486  S15
          56189  LIPOSOME?
     S16     52  S15 AND LIPOSOME?
? red

>>>Unrecognizable Command
? rd

...examined 50 records  (50)
...completed examining records
     S17     40  RD (unique items)
? t s17/3,ab/all


 17/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11627984   21436352   PMID: 11552228
  Liposomal anthracyclines for breast cancer.
  Sparano JA; Winer EP
  Department of Oncology, Montefiore Medical Center-Weiler Division, Bronx,
NY.
  Seminars in oncology (United States)  Aug 2001,  28  (4 Suppl 12)
 p32-40,  ISSN 0093-7754   Journal Code: UN5
  Languages: ENGLISH
  Document type: Journal Article
  Record type: In Process
  Doxorubicin and other anthracyclines are an important class of
agents for the treatment of early and advanced stage breast cancer,
but produce substantial acute and chronic toxicities. One strategy for
reducing anthracycline-associated toxicity is packaging them in
liposomes. Liposomes are closed vesicular structures that
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part, its AIDS-KS cellular cytotoxic effects by a redox-related mechanism, and provides a biochemical rationale for **doxorubicin**'s clinical efficacy in AIDS-KS **treatment**.

17/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09495516 95222599 PMID: 7707383
Reversal of multidrug resistance in human colon cancer cells expressing the human MDR1 gene by **liposomes** in combination with monoclonal antibody or verapamil.
Sela S; Husain SR; Pearson JW; Longo DL; Rahman A
Department of Medicine, Georgetown University, Washington, D.C. 20007, USA.
Journal of the National Cancer Institute (UNITED STATES) Jan 18 1995, 87 (2) p123-8, ISSN 0027-8874 Journal Code: J9J
Comment in J Natl Cancer Inst. 1995 Jan 18;87(2) 73-5
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
BACKGROUND: Colorectal cancer is a major cause of cancer-related mortality in the world and the second leading cause of neoplastic death in the United States. A major obstacle in the chemotherapy of this neoplasm is the emergence of multidrug resistance that is frequently associated with the expression of P-glycoprotein (p170) encoded by MDR1 (also known as PGY1) genes. Previously, we demonstrated that **liposome**-encapsulated **doxorubicin** is more cytotoxic than free **doxorubicin** in human promyelocytic leukemia and human breast cancer cells with the multidrug-resistant phenotype. PURPOSE: Our purpose was to investigate modulation of multidrug resistance by **liposome**-encapsulated **vincristine** (VCR) in a drug-resistant human colon cancer cell line HT-29mdr1 and the potentiation of this modulation in combination with monoclonal antibody MRK-16 or verapamil. METHODS: HT-29 parental cells and HT-29mdr1 cells were exposed to free VCR or **liposome**-encapsulated VCR alone or in combination with MRK-16 or verapamil. Cytotoxicity of cells after various **treatments** was determined by neutral red staining, and cellular content of VCR was measured by using radiolabeled VCR; p170 expression of cells was assessed by azidopine. RESULTS: HT-29mdr1 cells express a high amount of p170, thus conferring sixfold to sevenfold resistance to VCR compared with the parent cell line. **Liposome**-encapsulated VCR lowers drug resistance in HT-29mdr1 cells fourfold; IC50 values (concentration that causes 50% reduction in cell number) were 12.5 +/- 2.5 ng/mL compared with 42.5 +/- 5.0 ng/mL with free VCR. IC50 values for free VCR with empty **liposomes** were 25 +/- 1.25 ng/mL. The combination of MRK-16 and free VCR produced a twofold increase in cytotoxicity over free VCR in p170-expressing cells; the combination of MRK-16 and **liposome**-encapsulated VCR produced a 10-fold potentiation of cytotoxicity. toxicity. Nonspecific monoclonal antibody NR-LU-10 had no effect on cytotoxicity of HT-29mdr1 cells with free VCR or **liposome**-encapsulated VCR. The combination of 1.5 microM verapamil potentiated the cytotoxicity of free VCR ninefold to 10-fold, IC50 values reduced to 5.0 +/- 1.5 ng/mL, and in combination with **liposome**-encapsulated VCR, IC50 values reduced to 2.5 +/- 1.0 ng/mL, demonstrating a 15- to 17-fold potentiation of cytotoxicity. There were no significant differences in drug accumulation in HT-29mdr1 cells when **treated** with **liposome**-encapsulated VCR or free VCR. **Liposomes** inhibited the photoaffinity labeling of azidopine to p170 HT-29mdr1 cells. CONCLUSIONS: **Liposome** encapsulation of VCR effectively modulates multidrug resistance in human colon cancer cells and may become an important modality in **treatment** for colon cancers.

17/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

Tumor targeting using anti-her2 immunoliposomes

Park J.W.; Kirpotin D[redacted]; Hong K.; Shalaby R.; Shao Y.[redacted]ielsen U.B.; Marks J.D.; Papahadjopoulos D.; Benz C.C.

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Journal of Controlled Release (J. CONTROL. RELEASE) (Netherlands) 06 JUL 2001, 74/1-3 (95-113)

CODEN: JCREE ISSN: 0168-3659

PUBLISHER ITEM IDENTIFIER: S0168365901003157

DOCUMENT TYPE: Journal ; Conference Paper

LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 52

We have generated anti-HER2 (ErbB2) immunoliposomes (ILs), consisting of long circulating **liposomes** linked to anti-HER2 monoclonal antibody (MAb) fragments, to provide targeted drug delivery to HER2-overexpressing cells. Immunoliposomes were constructed using a modular strategy in which components were optimized for internalization and intracellular drug delivery. Parameters included choice of antibody construct, antibody density, antibody conjugation procedure, and choice of **liposome** construct. Anti-HER2 immunoliposomes bound efficiently to and internalized in HER2-overexpressing cells in vitro as determined by fluorescence microscopy, electron microscopy, and quantitative analysis of fluorescent probe delivery. Delivery via ILs in HER2-overexpressing cells yielded drug uptake that was up to 700-fold greater than with non-targeted sterically stabilized **liposomes**. In vivo, anti-HER2 ILs showed extremely long circulation as stable constructs in normal adult rats after a single i.v. dose, with pharmacokinetics that were indistinguishable from sterically stabilized **liposomes**. Repeat administrations revealed no increase in clearance, further confirming that ILs retain the long circulation and non-immunogenicity of sterically stabilized **liposomes**. In five different HER2-overexpressing xenograft models, anti-HER2 ILs loaded with **doxorubicin** (dox) showed potent anticancer activity, including **tumor** inhibition, regressions, and cures (pathologic complete responses). ILs were significantly superior vs. all other **treatment** conditions tested: free dox, liposomal dox, free MAb (trastuzumab), and combinations of dox+MAb or liposomal dox+MAb. For example, ILs produced significantly superior antitumor effects vs. non-targeted **liposomes** (P values from <0.0001 to 0.04 in eight separate experiments). In a non-HER2-overexpressing xenograft model (MCF7), ILs and non-targeted liposomal dox produced equivalent antitumor effects. Detailed studies of **tumor** localization indicated a novel mechanism of drug delivery for anti-HER2 ILs. Immunotargeting did not increase **tumor** tissue levels of ILs vs. **liposomes**, as both achieved very high **tumor** localization (7.0-8.5% of injected dose/g tissue) in xenograft **tumors**. However, histologic studies using colloidal-gold labeled ILs demonstrated efficient intracellular delivery in **tumor** cells, while non-targeted **liposomes** accumulated within stroma, either extracellularly or within macrophages. In the MCF7 xenograft model lacking HER2-overexpression, no difference in **tumor** cell uptake was seen, with both ILs and non-targeted **liposomes** accumulating within stroma. Thus, anti-HER2 ILs, but not non-targeted **liposomes**, achieve intracellular drug delivery via receptor-mediated endocytosis, and this mechanism is associated with superior antitumor activity. Based on these results, anti-HER2 immunoliposomes have been developed toward clinical trials. Reengineering of construct design for clinical use has been achieved, including: new anti-HER2 scFv F5 generated by screening of a phage antibody library for internalizing anti-HER2 phage antibodies; modifications of the scFv expression construct to support large scale production and clinical use; and development of methods for large-scale conjugation of antibody fragments with **liposomes**. We developed a scalable two-step protocol for linkage of scFv to preformed and drug-loaded **liposomes**. Our final, optimized anti-HER2 ILs-dox construct consists of F5 conjugated to

human IgGSUB1 heavy chain. This bivalent antibody-like molecule contains four N-glycosylation sites per polypeptide, three in the receptor portion and one in the Fc. The heterogeneous N-linked oligosaccharides of TNFR-IgG contain sialic acid (Sia), Gal, and GlcNAc as terminal sugar residues. To increase the level of terminal sialylation, we regalactosylated and/or resialylated TNFR-IgG using beta-1,4-galactosyltransferase (beta1,4GT) and/or **alpha**-2,3-sialyltransferase (alpha2,3ST). **Treatment** of TNFR-IgG with beta1,4GT and UDP-Gal, in the presence of MnClSUB2, followed by MALDI-TOF-MS analysis of PNGase F-released N-glycans showed that the number of oligosaccharides with terminal GlcNAc residues was significantly decreased with a concomitant increase in the number of terminal Gal residues. Similar **treatment** of TNFR-IgG with alpha2,3ST and CMP-sialic acid (CMP-Sia), in the presence of MnClSUB2, produced a molecule with an (similar)11% increase in the level of terminal sialylation but still contained oligosaccharides with terminal GlcNAc residues. When TNFR-IgG was **treated** with a combination of beta1,4GT and alpha2,3ST (either in a single step or in a stepwise fashion), the level of terminal sialylation was increased by (similar)20-23%. These results suggest that in vitro galactosylation and sialylation of therapeutic **glycoproteins** with terminal GlcNAc and Gal residues can be achieved in a single step, and the results are similar to those for the stepwise reaction. This type of in vitro glycosylation is applicable to other **glycoproteins** containing terminal GlcNAc and Gal residues and could prove to be useful in increasing the serum half-life of therapeutic **glycoproteins**.

7/3,AB/7 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE

07727872 EMBASE No: 1999205659
Suppressive effect of ethanol on the expression of hepatic **asialoglycoprotein** receptors augmented by interleukin-1beta, interleukin-6, and **tumor** necrosis factor-**alpha**

Kato J.; Mogi Y.; Kohgo Y.; Takimoto R.; Kobune M.; Hisai H.; Nakamura T.; Takada K.; Niitsu Y.
J. Kato, Fourth Department Internal Medicine, Sapporo Medical University, School of Medicine, South-1, West-16, Chuo-ku, Sapporo 060-8543 Japan

Journal of Gastroenterology (J. GASTROENTEROL.) (Japan) 1998, 33/6 (855-859)
CODEN: JOGAE ISSN: 0944-1174
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 26

Blood levels of inflammatory-related cytokines, including interleukin (IL)-1beta, IL-6, and **tumor** necrosis factor (TNF)-**alpha**, are elevated in patients with alcoholic liver diseases. We investigated the effects of these cytokines and ethanol on the expression of hepatic **asialoglycoprotein** receptors (AGPRs) in a human hepatoblastoma cell line, HepG2. An [sup 1sup 2sup 5I]-asialo-orosomucoid binding assay showed significant increases in surface AGPR numbers in HepG2 cells by **treatment** with IL-1beta, IL-6, and TNF-**alpha**, to levels which were approximately 130% of the values in untreated control cells. However, the enhanced AGPR numbers induced by **treatment** with these cytokines were markedly suppressed, to 70%-80% of the number in the untreated cells, by **treatment** with ethanol. Immunological detection of AGPR with a specific antibody demonstrated that the modulation of surface AGPR numbers was correlated with the cellular expression levels of AGPR. These results suggest that, although IL-1beta, IL-6, and TNF-**alpha** stimulate the synthesis of hepatic AGPR, ethanol suppresses the expression of AGPR augmented by these cytokines. This leads to an increase in serum asialo-orosomucoid levels caused by the disordered catabolism mediated by AGPR in patients with alcoholic liver disease.
? ds

derivatized PEG-PE linker and incorporated into commercially available liposomal **doxorubicin** (D[redacted]l(R)). Finally, further studies of the mechanism of action of anti-HER2 ILs-dox suggest that this strategy may provide optimal delivery of anthracycline-based chemotherapy to HER2-overexpressing cancer cells in the clinic, while circumventing the cardiotoxicity associated with trastuzumab+anthracycline. We conclude that anti-HER2 immunoliposomes represent a promising technology for **tumor** -targeted drug delivery, and that this strategy may also be applicable to other receptor targets and/or using other delivered agents.

17/3,AB/20 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE

11189016 EMBASE No: 2001208000
Pegylated liposomal **doxorubicin**: Metamorphosis of an old drug into a new form of chemotherapy
Gabizon A.A.
Dr. A.A. Gabizon, Department of Oncology, Hadassah Medicai Center, POB 12000, Kiryat Hadassah, Jerusalem il-91120 Israel
AUTHOR EMAIL: alberto@md2.huji.ac.il
Cancer Investigation (CANCER INVEST.) (United States) 2001, 19/4 (424-436)
CODEN: CINVD ISSN: 0735-7907
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 76

Pegylated liposomal **doxorubicin** (Doxil, Caelyx) is a formulation of **doxorubicin** in poly(ethylene glycol)-coated (stealth) **liposomes** with a prolonged circulation time and unique toxicity profile. We review the preclinical and clinical pharmacology as well as recent clinical data obtained in specific cancer types. Doxil **liposomes** retain the drug payload during circulation and accumulate preferentially in tissues with increased microvascular permeability, as often is the case of **tumors**. Doxil toxicity profile is drastically different from that of **doxorubicin**, and is characterized by dominant and dose-limiting mucocutaneous toxicities, mild myelosupression, minimal alopecia, and no apparent cardiac toxicity. Although the single maximum tolerated dose (MTD) of Doxil is actually lower than that of conventionally administered **doxorubicin**, the cumulative MTD dose of Doxil may be substantially greater than that of free **doxorubicin**. Doxil is probably one of the most active agents in AIDS-related Kaposi's sarcoma and has a definite role in management of recurrent ovarian cancer. The potential of Doxil in the **treatment** of other cancer types and the opportunities it offers in combination with other drugs and therapeutic modalities are under active investigation.

17/3,AB/21 (Item 3 from file: 72)
DIALOG(R)File 72:EMBASE

11133944 EMBASE No: 2001148869
Chemotherapy of metastatic breast cancer: What to expect in 2001 and beyond
Esteva F.J.; Valero V.; Pusztai L.; Boehnke-Michaud L.; Buzdar A.U.; Hortobagyi G.N.
Dr. F.J. Esteva, Dept. of Breast Medical Oncology, Univ. Texas M.D. Anderson Can. Ctr., Box 56, 1515 Holcombe Blvd., Houston, TX 77030 United States
AUTHOR EMAIL: festeva@mdanderson.org
Oncologist (ONCOLOGIST) (United States) 2001, 6/2 (133-146)

CODEN: OCOLF ISSN: 1023-7159
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 111

Chemotherapy plays an important role in the management of metastatic breast cancer. The anthracyclines (**doxorubicin**, epirubicin) and the taxanes (paclitaxel, docetaxel) are considered the most active agents for patients with advanced breast cancer. Traditionally, the anthracyclines have been used in combination with cyclophosphamide and 5-fluorouracil (FAC, FEC). The taxanes have single-agent activity similar to older combination chemotherapy **treatments**. There is great interest in developing anthracycline/taxane combinations. Capecitabine is indicated for patients who progress after anthracycline and taxane therapy. Vinorelbine and gemcitabine have activity in patients with metastatic breast cancer and are commonly used as third- and fourth-line palliative therapy. The role of high-dose chemotherapy is not well-defined and remains experimental. Novel cytotoxic therapy strategies include the development of anthracycline, taxane, and oral fluoropyrimidine analogues; antifolates; topoisomerase I inhibitors, and multidrug resistance inhibitors. A better understanding of the biology of breast cancer is providing novel **treatment** approaches. Oncogenes and **tumor**-supressor genes are emerging as important targets for therapy. Trastuzumab, a monoclonal antibody directed against the Her-2/neu protein, has been shown to prolong survival in patients with metastatic breast cancer. Other novel biologic therapies interfere with signal transduction pathways and angiogenesis. The challenge for the next decade will be to integrate these promising agents in the management of metastatic and primary breast cancer.

17/3,AB/22 (Item 4 from file: 72)
DIALOG(R)File 72:EMBASE

10782288 EMBASE No: 2000262699
Molecular and pharmacokinetic properties associated with the therapeutics of Bcl-2 **antisense** oligonucleotide G3139 combined with free and liposomal **doxorubicin**
De Menezes D.E.L.; Hudon N.; McIntosh N.; Mayer L.D.
L.D. Mayer, Department of Advanced Therapeutics, British Columbia Cancer Res. Centre, 601 West 10th Avenue, Vancouver, BC V5Z 4E6 Canada
AUTHOR EMAIL: lmayer@bccancer.bc.ca
Clinical Cancer Research (CLIN. CANCER RES.) (United States) 2000, 6/7 (2891-2902)
CODEN: CCREF ISSN: 1078-0432
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 40

Bcl-2 is a key apoptosis-regulating protein that has been implicated in mechanisms of chemoresistance for a variety of malignancies by blocking programmed cell death. This study investigated the activity of the Bcl-2 **antisense** oligodeoxynucleotide (AS ODN) G3139 combined with free **doxorubicin** (F-DOX) or sterically stabilized liposomal **doxorubicin** (SL-DOX) to determine the role that drug pharmacodistribution properties may have on antitumor activity using a Bcl-2-expressing human breast solid **tumor** xenograft model. Administration of G3139 was able to delay the growth of MDA435/LCC6 cells compared with control ODN-**treated** animals; however, in all of the cases, **tumors** reestablished after AS ODN **treatment**. Western blot analyses of Bcl-2 levels of solid **tumors** showed a sequence-specific down-regulation of the Bcl- 2 protein after four daily doses of G3139, which correlated with histological evidence of **tumor** cell death. interestingly, the expression of Bcl-2 returned to pretreatment levels during the course of subsequent ODN administration, which suggested

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Set     Items   Description
S1      37199   GLYCOPROTEIN? AND (ALPHA OR ALPHA (W) 1)
S2      65301   DOXORUBICIN?
S3     102168   S1 OR S2
S4      15964   S3 AND TUMOR? AND TREAT?
S5          0   S4 AND DESIALYAT?
S6          7   S4 AND ASIALOGLYCOPROTEIN?
S7          7   RD (unique items)
? s s4 and agpr and doxorubicin?

          15964  S4
             30  AGPR
          65301  DOXORUBICIN?
      S8      0  S4 AND AGPR AND DOXORUBICIN?
? s desialyated and glycoprotein?

             49  DESIALYATED
         240684  GLYCOPROTEIN?
      S9     19  DESIALYATED AND GLYCOPROTEIN?
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...completed examining records
     S10     16  RD (unique items)
? s s10 and tumor?

             16  S10
        1377188  TUMOR?
     S11      2  S10 AND TUMOR?
? t s11/3,ab/all


 11/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09696837   98183442   PMID: 9514919
  Detection of the asialoglycoprotein receptor on cell lines of
extrahepatic origin.
  Park JH; Cho EW; Shin SY; Lee YJ; Kim KL
  Peptide Engineering Research Unit, Korea Research Institute of Bioscience
and Biotechnology, Taejon, South Korea.
  Biochemical and biophysical research communications (UNITED STATES)  Mar
6 1998,  244  (1)  p304-11,  ISSN 0006-291X  Journal Code: 9Y8
  Languages: ENGLISH
  Document type: Journal Article
  Record type: Completed
  The asialoglycoprotein receptor (ASGPR) is the first lectin discovered in
mammals. Despite its significant biological role in binding and
internalization of desialyated glycoproteins, at least in the
human, little information is available regarding its tissue distribution
outside of the liver. In the present study, antibodies were raised against
the H1 major subunit of the human ASGPR using synthetic peptide antigens,
and their binding specificity confirmed by enzyme linked immunosorbent
assay. Cell surface analysis by fluorescence activated flow cytometry on
various human tissue cell lines confirmed the liver parenchymal cells as
the major expression site of ASGPR. Nonetheless, ASGPR was also detectable
on some extrahepatic cells such as the Jurkat T-cell line. The
determination of extrahepatic expression of ASGPR will have consequences in
analyzing the biological role of this receptor complex as well as having
implications in designing ASGPR mediated drug- or gene-delivery strategies.


 11/3,AB/2     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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? s s13 and ((avidin and biotin) or (thiol and maleamide))

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            244  S13
          16179  AVIDIN
          35253  BIOTIN
          36834  THIOL
             11  MALEAMIDE
    S14       1  S13 AND ((AVIDIN AND BIOTIN) OR (THIOL AND MALEAMIDE))
? t s14/3,ab/all
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14/3,AB/1 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

06701618 EMBASE No: 1996366565
Therapeutic opportunities for targeted liposomal drug delivery
Allen T.M.; Moase E.H.
Department of Pharmacology, University of Alberta,Edmonton, Alta. T6G 2H7 Canada
Advanced Drug Delivery Reviews (ADV. DRUG DELIV. REV.) (Netherlands) 1996, 21/2 (117-133)
CODEN: ADDRE ISSN: 0169-409X
PUBLISHER ITEM IDENTIFIER: S0169409X96004024
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

One way to increase the therapeutic index of drugs such as anticancer drugs, which have low therapeutic indices would be by specifically targeting the drugs to the diseased cells. This can be accomplished by associating the drugs with **liposomes** and coupling a targeting antibody or ligand to the **liposome** surface. A variety of coupling methods can be used to attach antibodies or ligands to the **liposomes**, and, to date, the best targeting results have been obtained when the targeting moiety is attached at the terminus of a hydrophillic polymer such as polyethylene glycol (PEG). Targeted **liposomes** have been demonstrated to have specific binding and increased cytotoxicity to cells in vitro compared to non-targeted **liposomes**. The best therapeutic results in vivo have been obtained to date when the **liposomes** are targeted to cells easily accessible within the vasculature, or to micrometastatic cells. **Treatment** of more advanced solid tumours with targeted **liposomes** presents a challenge to overcome the 'binding site barrier' at the tumour surface. Evidence is accumulating that targeting to internalizing receptors is more successful than targeting to

envelop water-soluble molecules. They may serve as vehicles for delivering cytotoxic agents more specifically to **tumor**, and limit exposure of normal tissues to the drug. Liposomal anthracyclines are more effective and less toxic in a number of preclinical models compared with conventional anthracyclines. Several liposomal anthracyclines have been extensively studied in humans with a variety of cancer types, including TLC D-99 (Myocet; The **Liposome** Company, Elan Corporation, Princeton, NJ), liposomal **daunorubicin** (Daunoxome; NeXstar Pharmaceuticals, Inc, San Dimas, CA), and pegylated liposomal **doxorubicin** (Doxil; Alza Pharmaceuticals, Palo Alto, CA, Caelyx; Schering Corporation, Kenilworth, NJ). Although none of these agents are currently approved for the **treatment** of breast cancer in the United States, the liposomal **doxorubicin** preparations seem to have comparable activity and less cardiac toxicity than conventional **doxorubicin**. Furthermore, they have been safely combined with other cytotoxic agents, including cyclophosphamide, 5-fluorouracil, vinorelbine, paclitaxel, and docetaxel. Further studies will be required do determine their role in the **treatment** of breast cancer. Semin Oncol 28 (suppl 12):32-40.

17/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10840287 20370423 PMID: 10914739

Molecular and pharmacokinetic properties associated with the therapeutics of bcl-2 **antisense** oligonucleotide G3139 combined with free and liposomal **doxorubicin**.

Lopes de Menezes DE; Hudon N; McIntosh N; Mayer LD
Department of Advanced Therapeutics, British Columbia Cancer Research Centre, Vancouver, Canada.

Clinical cancer research (UNITED STATES) Jul 2000, 6 (7) p2891-902, ISSN 1078-0432 Journal Code: C2H
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Bcl-2 is a key apoptosis-regulating protein that has been implicated in mechanisms of chemoresistance for a variety of malignancies by blocking programmed cell death. This study investigated the activity of the Bcl-2 **antisense** oligodeoxynucleotide (AS ODN) G3139 combined with free **doxorubicin** (F-DOX) or sterically stabilized liposomal **doxorubicin** (SL-DOX) to determine the role that drug pharmacodistribution properties may have on antitumor activity using a Bcl-2-expressing human breast solid **tumor** xenograft model. Administration of G3139 was able to delay the growth of MDA435/LCC6 cells compared with control ODN-**treated** animals; however, in all of the cases, **tumors** reestablished after AS ODN **treatment**. Western blot analyses of Bcl-2 levels of solid **tumors** showed a sequence-specific down-regulation of the Bcl-2 protein after four daily doses of G3139, which correlated with histological evidence of **tumor** cell death. Interestingly, the expression of Bcl-2 returned to pretreatment levels during the course of subsequent ODN administration, which suggested the development of resistance to continued Bcl-2 ODN **treatment**. The antitumor activity of ODN given in conjunction with either F-DOX or SL-DOX was also examined. The combination of G3139 and F-DOX was able to suppress the growth of MDA435/LCC6 cells beyond that obtained with either of the **treatments** given alone, indicative of synergistic action. Examination of the pharmacokinetics of F-DOX with systemic G3139 administration revealed that elevated **tumor** drug DOX levels were obtained compared with DOX **treatment** in the absence of G3139. This effect was sequence-specific and plasma DOX levels were unaffected by G3139 **treatment**, which indicated possible positive ODN-drug interactions at the **tumor** site. Combining G3139 with SL-DOX further increased the degree of antitumor activity. The improved efficacy of this combination was attributed to increased **tumor** drug levels that arise from the ability

of SL-DOX to passively accumulate in solid **tumors**. These results suggest that additional benefits of Bcl-2 **antisense** ODN may be obtained when it is combined with liposomal formulations of anticancer drugs such as DOX.

17/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10800549 99164506 PMID: 10065112
Liposomal **daunorubicin**: in vitro and in vivo efficacy in multiple myeloma.
Pratt G; Wiles ME; Rawstron AC; Davies FE; Fenton JA; Proffitt JA; Child JA; Smith GM; Morgan GJ
Department of Haematology, General Infirmary at Leeds, U.K.
Hematological oncology (ENGLAND) Jun 1998, 16 (2) p47-55, ISSN 0278-0232 Journal Code: GB2
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Liposomal encapsulation of anthracyclines is a potential method of drug targeting, altering both the antitumour activity and side-effect profile of anthracyclines. Liposomal **daunorubicin** (daunoxome) shows both altered pharmacokinetics and a potential for reducing dose-limiting cardiotoxicity compared to conventional **daunorubicin**. Anthracyclines have a common role in the **treatment** of multiple myeloma, a prevalent and fatal haematological malignancy. Avoiding cumulative anthracycline toxicity in these patients is important. There is also a need for more effective relapse schedules given that many patients have chemosensitive disease at relapse. We have analysed daunoxome in vitro in myeloma cell lines using a thymidine-based cytotoxicity assay and show superior efficacy compared to a pegylated liposomal **doxorubicin** derivative. Subsequently we have **treated** seven relapsed myeloma patients with a regime consisting of oral CCNU 25-50 mg/m2 on day 1, 4 days of oral dexamethasone 10 mg/m2 and intravenous daunoxome (liposomal **daunorubicin**) given for 4 days (total 100 mg/m2). The main toxicity was myelosuppression but non-haematological toxicity was minimal and the regime was well tolerated. Four out of seven of these heavily pretreated patients responded. Together with the in vitro data on its cytotoxicity in myeloma and its favourable pharmacokinetic profile further studies of liposomal **daunorubicin** in myeloma would be warranted.

17/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10748747 98281051 PMID: 9619752
Reversal of multidrug resistance by a **liposome**-MDR1 **ribozyme** complex.
Masuda Y; Kobayashi H; Holland JF; Ohnuma T
Samuel Bronfman Department of Medicine, Mount Sinai School of Medicine, New York, NY 10029, USA.
Cancer chemotherapy and pharmacology (GERMANY) 1998, 42 (1) p9-16, ISSN 0344-5704 Journal Code: C9S
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
PURPOSE: Multidrug resistance (MDR) is a major obstacle in cancer chemotherapy. We examined whether cationic **liposome**-mediated transfer of a **ribozyme** could reverse MDR. METHODS: A **ribozyme** which cleaved codon 196 of MDR1 mRNA was constructed from synthetic oligonucleotides. The MDR1 **ribozyme** was mixed with N-(1-(2,3-dileoyloxy)propyl)-N,N,N-trimethylammonium methyl sulfate (DOTAP) to form a liposomal complex. The complex was used to **treat** two P-glycoprotein-producing MDR cell lines: MCF-7/R human breast cancer cells

resistant to **doxorubicin** and MOLT-3/TMQ800 human ALL cells resistant to trimetrexate (TMQ). In order to investigate the differential sensitivity of these two cell lines to the **liposome-ribozyme** complex, cellular pharmacological studies including phase-contrast and confocal microscopic studies were performed. RESULTS: **Treatment** with the **liposome-ribozyme** complex resulted in reversal of **vincristine** (VCR) resistance in MCF-7/R cells, but not in MOLT-3/TMQ800 cells. In MCF-7/R cells the **treatment** resulted in decreases in MDR1 mRNA expression and P-glycoprotein production, whereas no changes in these parameters were seen in MOLT-3/TMQ800 cells. Phase-contrast microscopy revealed that in MCF-7/R cells **treatment** with DOTAP led to the formation of cytoplasmic vacuoles, and **treatment** with latex beads resulted in the development of a shiny material in the cytoplasm. In contrast, in MOLT-3/TMQ800 cells hardly any morphological changes occurred. Confocal microscopic imaging showed cytoplasmic fluorescence in MCF-7/R cells after **treatment** with DOTAP/FITC-dextran or FITC-conjugated latex beads. In MOLT-3/TMQ800 cells no fluorescence was detected. **Treatment** with cytochalasin B abolished fluorescence in MCF-7/R cells after **treatment** with DOTAP/FITC-dextran or FITC-conjugated latex beads. These studies show that MCF-7/R cells have high endocytotic activity whereas MOLT-3/TMQ800 cells have little activity. CONCLUSIONS: Endocytotic activity was correlated with the success of cationic **liposome**-mediated transfer of MDR1 **ribozyme** . Determination of endocytotic activity of target **tumor** cells may be predictive of efficacy of **liposome**-mediated gene transfer.

17/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10744826 98053892 PMID: 9393743

Liposomal **doxorubicin** circumvents PSC 833-free drug interactions, resulting in effective therapy of multidrug-resistant solid **tumors**.

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Department of Medical Oncology (Advanced Therapeutics), British Columbia Cancer Agency, Vancouver, Canada.

Cancer research (UNITED STATES) Dec 1 1997, 57 (23) p5246-53, ISSN 0008-5472 Journal Code: CNF
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Conventional methods that are used to overcome multidrug resistance (MDR) often involve the coadministration of chemosensitizers and anticancer drugs. The cyclosporin analogue SDZ PSC 833 [(3'-keto-Bmt1)-(Val2)-cyclosporin] (PSC 833) has been shown to possess powerful chemosensitization properties in vitro, in addition to being intrinsically nontoxic. However, coadministration of PSC 833 with anticancer drugs, such as **daunorubicin**, **doxorubicin** (DOX), and Taxol, have resulted in the exacerbation of anticancer drug toxicity, which is due to altered anticancer drug pharmacokinetics. Here, we hypothesized that optimization of the anticancer drug delivery, using liposomal carriers, may, by avoiding these adverse interactions, offer a significant advantage over nonencapsulated drugs. Toxicity studies were conducted in normal BDF1 mice, with i.v. DOX (free or **liposome** encapsulated) administration and p.o. PSC 833 in single and multiple dosage regimens over a 15-day study period. p.o. administration of PSC 833, at a dose of 100 mg/kg, reduced the maximum tolerated dose (MTD) of i.v administered free drug by 2.5-3-fold, in single- and multiple-dose regimens. In contrast, PSC 833 administration resulted in only a 20% reduction of the MTD for DOX encapsulated in 100-nm 1,2 distearoyl-sn-glycero-3-phosphocholine/cholesterol **liposomes** (55:45 molar lipid ratio) in a single-dose regimen and had no effect on the liposomal DOX MTD for the day 1, 5, and 9 **treatment** schedule. Modest modulation of P-glycoprotein-mediated MDR was observed in the murine P388/ADR solid **tumor** model when PSC 833 was administered with free DOX at the MTD. In contrast, liposomal DOX combined with PSC 833 resulted

in **tumor** growth inhibition that was comparable to that observed for drug-sensitive P388/WT t[redacted]rs. This efficacy of P388/ADR [redacted]ors **treatment** was dependent on PSC 833 because **treatment** with liposomal DOX alone provided significantly less antitumor activity. Pharmacokinetic and tissue distribution data demonstrated that DOX encapsulated in 1,2 distearoyl-sn-glycero-3-phosphocholine/cholesterol **liposomes** exhibited comparable plasma elimination and tissue distribution properties in the presence and absence of PSC 833, whereas free DOX displayed reduced plasma elimination rates and altered tissue distribution in the presence of PSC 833. These results provide evidence that PSC 833 can induce P-glycoprotein modulation and chemosensitize MDR **tumors** in the absence of altered DOX pharmacokinetics when liposomal carriers are used. This suggests that the improved **tumor** selectivity of anticancer drugs that are administered in liposomal formulations may avoid the complications that are associated with free drug-MDR-reversing agent combinations and enhance the therapy of multidrug-resistant **tumors**.

17/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10157815 99241928 PMID: 10227389

Thiol redox modulation of **doxorubicin** mediated cytotoxicity in cultured AIDS-related Kaposi's sarcoma cells.

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Journal of cellular biochemistry (UNITED STATES) May 1 1999, 73 (2) p259-77, ISSN 0730-2312 Journal Code: HNF

Contract/Grant No.: CA U01 66531, CA, NCI; DE R01 12183, DE, NIDCR; HL R01 52793, HL, NHLBI

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

The chemotherapeutic, **doxorubicin**, is currently used empirically in the **treatment** of AIDS- related Kaposi's sarcoma (AIDS-KS). Although often employed in a chemotherapeutic cocktail (**doxorubicin**, bleomycin, **vincristine**) single-agent therapy has recently been attempted with **liposome** encapsulated **doxorubicin**. Although **doxorubicin**'s mechanism of action against AIDS-KS is unknown, we hypothesized that **doxorubicin**'s ability to undergo redox cycling is associated with its clinical efficacy. The current study was conducted to investigate the effects of **doxorubicin** on selected xenobiotic-associated biochemical responses of three cellular populations: KS lesional cells, nonlesional cells from the KS donors, and fibroblasts obtained from HIV- aged matched men. Our results show that during **doxorubicin** challenge, there are strong positive correlations between cellular glutathione (GSH) levels and viability ($r = 0.94$), NADPH levels and viability ($r = 0.93$), and GSH and NADPH levels ($r = 0.93$), and demonstrate that as a consequence of their abilities to maintain cellular thiol redox pools HIV- donor cells are significantly less susceptible to **doxorubicin**'s cytotoxic effects relative to AIDS-KS cells. Additional studies further supported the contribution of reduced thiols in mediating **doxorubicin** tolerance. While pretreatment with the GSH precursor, N-acetylcysteine was cytoprotective for all cell groups during **doxorubicin** challenge, GSH depletion markedly enhanced **doxorubicin**'s cytotoxic effects. Studies to investigate the effects of a hydroxyl scavenger and iron chelator during **doxorubicin** challenge showed moderate cytoprotection in the AIDS-KS cells but deleterious effects in the HIV control cells. Inactivation of the longer lived membrane generated ROI in the cytoprotective deficient AIDS-KS cells, as well as an impairment of endogenous defenses in the HIV- donor control cells, may account for these scavenger and chelator associated findings. In summary, our findings show that **doxorubicin** mediates, at least in

08094492 93328349 PM[redacted] 8335404
Therapy of mouse mammary carcinomas with **vincristine** and **doxorubicin** encapsulated in sterically stabilized **liposomes**.
Vaage J; Donovan D; Mayhew E; Uster P; Woodle M
Department of Experimental Pathology, Roswell Park Cancer Institute, Buffalo, NY 14263.
International journal of cancer. Journal international du cancer (UNITED STATES) Jul 30 1993, 54 (6) p959-64, ISSN 0020-7136 Journal Code: GQU
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
This study tested the therapeutic effects of **vincristine** sulfate and **doxorubicin** hydrochloride, each drug in 2 different formulations: (i) as a solution in saline, and (ii) encapsulated in sterically stabilized, long-circulating **liposomes** composed of hydrogenated soy-phosphatidylcholine/cholesterol/polyethylene-glycerol-disteroyl++ +- phosphatidylethanolamine. The 4 drug preparations were used to **treat** s.c. implants of the mouse mammary carcinoma MC2. The drugs were given by i.v. injection over 15 to 18 days, starting 3 days after **tumor** implantation. The single-drug therapeutic effects of **vincristine** (S-VCR) and **doxorubicin** (Doxil) in **liposomes** were compared, and the 2 preparations were also tested in alternate and in simultaneous combinations. These new **liposome** formulations of **vincristine** and **doxorubicin** were significantly more effective than the free drugs in curing the mice. Alternate, semi-weekly injection of both drugs gave the best therapeutic effect. Prolonged circulation time with increased accumulation in **tumors** are considered likely reasons for the improved therapeutic efficacy of both drugs when encapsulated in these **liposomes**.

17/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08092171 93231451 PMID: 8097173
Modulation of **doxorubicin** resistance in multidrug-resistant cells by **liposomes**.
Thierry AR; Vige D; Coughlin SS; Belli JA; Dritschilo A; Rahman A
Department of Radiation Medicine, Georgetown University School of Medicine, Washington, D.C. 20007.
FASEB journal (UNITED STATES) Apr 1 1993, 7 (6) p572-9, ISSN 0892-6638 Journal Code: FAS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
In this study, we have confirmed the ability of **liposome** -encapsulated **doxorubicin** to modulate drug resistance, as previously observed in CH LZ cells (Thierry et al., Cancer Commun. 1, 311-316, 1989), in two human multidrug-resistant (MDR) cell lines, the breast cancer MCF-7/ADR cell line, and the ovarian carcinoma SKVLB cell line. This effect was specific to MDR cells, as liposomally encapsulated **doxorubicin** did not enhance cell sensitivity to the drug in the parental cell lines. Cytotoxicity assays demonstrated that empty **liposomes** in the presence of free **doxorubicin** (Dox) reversed resistance to the drug at a level that may be higher than that observed when **liposome**-encapsulated Dox is used. This effect seems to be due to the high affinity of Dox for cardiolipin, one of the **liposome** components, which leads to the association of the drug and the cardiolipin-containing **liposomes** in the culture medium before entry into the cells. Neither pretreatment of empty **liposomes** before drug **treatment** nor combined incubation of **vincristine** and empty **liposomes** alter MDR in CH LZ cells, suggesting that the drug must be encapsulated or complexed to the **liposomes** to overcome MDR. Because MDR in CH LZ cells does not seem

to be related to GSH level, MDR modulation by **liposome**-encapsulated Dox apparently may not be effected by altering the [redacted] function. These results suggest that the enhancement of sensitivity of MDR cells using Dox encapsulated in **liposomes** or complexed with **liposomes** may be explained by an increase in cell drug incorporation and by an intracellular drug redistribution. Fluorescence confocal microscopy study indicated that Dox is transported and distributed mainly in intracytoplasmic vesicles in SKVLB and MCF-7/ADR cells, whereas in parental cells the drug is located mainly in the nucleus. In addition, presentation of Dox in **liposomes** modifies the drug distribution pattern in MDR cells by partially shifting the drug to nuclear compartments. Thus, **liposome**-associated Dox may bypass the vesicular drug transport in MDR cells, resulting in the enhancement of the drug biological activity.

17/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08064183 90304775 PMID: 2194651
Anthracycline antibiotics with high **liposome** entrapment: structural features and biological activity.
Perez-Soler R; Priebe W
Department of Clinical Immunology and Biological Therapy, University of Texas M. D. Anderson Cancer Center, Houston 77030.
Cancer research (UNITED STATES) Jul 15 1990, 50 (14) p4260-6, ISSN 0008-5472 Journal Code: CNF
Contract/Grant No.: CA-45423, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We evaluated the entrapment of 21 different water-insoluble aglycones or anthracycline antibiotics in multilamellar **liposomes** composed of dimyristoyl phosphatidyl choline and dimyristoyl phosphatidyl glycerol at a 7:3 molar ratio. The drug:lipid weight ratio was 1:15 to 1:50. The different analogues tested were modified at position 4 in the aglycone portion (4-demethoxy) and/or positions 2' (halo), 3' (hydroxy, acetoxy), or 4' (epi, acetoxy) in the sugar portion. The entrapment efficiency was assessed by measuring the amount of free drug remaining in the supernatant after centrifugation of the **liposomes** and by direct examination of the pellets by fluorescent microscopy. Optimal entrapment (greater than 98%) was observed with only four compounds: 4-demethoxyadriamycinone; 2'-iododaunorubicin; 4-demethoxydaunorubicin; and 2'-iodo-3'-hydroxy-4'-epi -4-demethoxydoxorubicin (Compound 22). All other compounds showed significant drug precipitation outside the multilamellar vesicles when observed by fluorescent microscopy. Compound 22, entrapped in **liposomes** , was evaluated in vivo against i.p. L-1210 leukemia by the i.p. route, and liver metastases of M5076 reticulosarcoma by the i.v. route. In both models, **liposome**-entrapped Compound 22 was more active than **doxorubicin** at the optimal dose [median survival (given in percentage) of **treated** to control animals was for L-1210, greater than 600 versus 212; for M5076, 200 versus 133]. 4-Demethoxy and 2'-iodo are structural modifications that markedly enhance the affinity of anthracycline antibiotics for lipid bilayers without compromising biological activity. These findings will serve as a guideline to obtain **liposome** -anthracycline preparations, with optimal formulation characteristics, enhanced **tumor** -targeting properties, and non-cross-resistance with **doxorubicin**.

17/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07183088 93095130 PMID: 1361008
Liposome-mediated modulation of multidrug resistance in human HL-60 leukemia cells.

Rahman A; Husain SR; Siddiqui J; Verma M; Agresti M; Center M; Safa AR; Glazer RI

Department of Medicine, Vincent T. Lombardi Cancer Research Center, Georgetown University Medical Center, Washington, D.C.

Journal of the National Cancer Institute (UNITED STATES) Dec 16 1992, 84 (24) p1909-15, ISSN 0027-8874 Journal Code: J9J

Languages: ENGLISH

Document type: Journal Article

Record type: Completed

BACKGROUND: Multidrug resistance (MDR) is a major obstacle in cancer **treatment**. Resistance of cultured **tumor** cells to major classes of cytotoxic drugs is frequently due to expression of a plasma membrane P-glycoprotein encoded by MDR genes. We have demonstrated that **liposome**-encapsulated **doxorubicin** is more toxic than the free drug and that it modulates MDR in Chinese hamster LZ cells and human colon cancer cells. PURPOSE: To investigate further the association between expression of P-glycoprotein and modulation of MDR by **liposome** -encapsulated **doxorubicin**, we studied **vincristine**-resistant HL-60/VCR leukemia cells, which express P-glycoprotein, and **doxorubicin** -resistant HL-60/ADR leukemia cells, which do not. METHODS: Cells were exposed to various concentrations of free **doxorubicin** and **liposome**-encapsulated **doxorubicin**. The cellular content of **doxorubicin** was determined by fluorescence analysis, and cytotoxicity was determined by cell growth inhibition. Photoaffinity-labeling studies of P-glycoprotein binding were performed on HL-60/VCR and HL-60/ADR cells and KB-GSV2 cells transfected with the MDR1 gene (also known as PGY1). RESULTS: The concentrations that caused 50% inhibition of growth (IC50) for free **doxorubicin** in HL-60, HL-60/ADR, and HL-60/VCR cells were 30 nM, 9 microM, and 0.9 microM, respectively. The values for **liposome**-encapsulated **doxorubicin** in parental HL-60 cells and HL-60/ADR cells were 20 nM and 9 microM, respectively, indicating little or no sensitization. In contrast, HL-60/VCR cells were fivefold more sensitive to **liposome**-encapsulated **doxorubicin** than to free **doxorubicin** , and IC50 was reduced to 0.17 microM. In HL-60 cells exposed to **liposome**-encapsulated **doxorubicin**, intracellular **doxorubicin** accumulation was less than that seen with free drug. In contrast, in HL-60/VCR cells, accumulation was twofold to threefold higher than that with free **doxorubicin**. **Liposome**-encapsulated **doxorubicin** completely inhibited the photoaffinity labeling of P-glycoprotein by azidopine in membrane vesicles of HL-60/VCR cells, with a potency comparable to that of azidopine, suggesting that circumvention of MDR by **liposomes** is related to their specific interaction with P-glycoprotein. The studies with KB-GSV2 cells indicated that blank **liposomes** can directly inhibit photoaffinity labeling of P-glycoprotein. CONCLUSIONS: These results demonstrate the effectiveness of **liposome**-encapsulated **doxorubicin** in overcoming resistance in the multidrug-resistant phenotype of HL-60/VCR cells by direct interaction with P-glycoprotein. Furthermore, they indicate that **liposome** -encapsulated **doxorubicin** may be an effective **treatment** for human cancers.

17/3,AB/12 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12775467 BIOSIS NO.: 200000529090
Designing liposomal anticancer drug formulations for specific therapeutic applications.
AUTHOR: Mayer Lawrence D(a); Krishna Rajesh; Webb Murray; Bally Marcel
AUTHOR ADDRESS: (a)Department of Advanced Therapeutics, BC Cancer Agency, 600 West 10th Ave., Vancouver, BC, V5Z 4E6**Canada
JOURNAL: Journal of Liposome Research 10 (2-3):p99-115 May-August, 2000
MEDIUM: print
ISSN: 0898-2104

OK

DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

2000 OK

ABSTRACT: Liposomal drug delivery systems have progressed significantly over the past 10 years, where technical barriers to the development of **liposome**-based pharmaceutical agents have been largely overcome and the clinical benefits of such systems have been established in several disease applications, particularly for cancer chemotherapy. We now have the ability to design sophisticated liposomal drug delivery systems with multifunctional properties including steric stabilizing lipids, targeting ligands, pH and temperature sensitive lipid compositions as well as components that induce intracellular delivery. However, the design of **liposomes** that exhibit optimized therapeutic activity will depend on the specific disease application as well as the chemical and biophysical properties of the pharmacological agent to be delivered. This is highlighted by the correlation between **liposome** physical characteristics and their biological behaviour as delivery systems for the anticancer drugs **vincristine** and **doxorubicin**. For **doxorubicin**, both EPC-based conventional and saturated, sterically stabilized **liposome** formulations have been shown to be effective against a wide variety of **tumor** types and their clinical utility has been firmly established. It is unclear at this time which formulation may be most effective for **treating** specific **tumor** types. This is somewhat surprising since the two commercial formulations exhibit very different biophysical and pharmacokinetic properties. However, in the case of combined therapy with modulators of P-glycoprotein such as PSC 833 we have observed a significant difference in toxicity and efficacy properties between these two formulations. **Doxorubicin** encapsulated inside EPC/cholesterol **liposomes** was adversely affected by co-administration with PSC 833 whereas DSPC/cholesterol/DSPE-PEG formulations were minimally affected. This was related to the increased drug leakage observed for the EPC/cholesterol system which resulted in elevated circulating free **doxorubicin** due to PSC 833-induced impairment of drug excretion. As a result, EPC/cholesterol **doxorubicin** displayed a reduced maximum tolerated dose with PSC 833 administration and modest antitumor activity against multidrug resistant (MDR) human breast **tumor** xenografts. In contrast, the sterically stabilized formulation could be administered at full dose, resulting in complete reversal of MDR and significant atitumor activity. **Vincristine** is a cell cycle specific whose antitumor potency increases dramatically with increased duration of exposure. The therapeutic activity of **liposome** formulations of this drug against solid **tumor** appears most dependent on retention of **vincristine** in the **liposomes**. Increasing the order of the **liposome** bilayer by moving from egg phosphatidylcholine (EPC) to distearoyl PC (DSPC) and finally sphingomyelin (SM) dramatically increases therapeutic activity and is associated with increased drug retention in the **liposomes** after iv administration. For these systems, incorporation of PEG-derivatized steric stabilizing lipids increased **liposome** circulation longevity, but decreased drug retention, resulting in no net improvement of efficacy. Consequently, for this drug conventional **liposomes** composed of SM and cholesterol appear to provide the optimum therapeutic index. Taken together, the results described above highlight the importance of designing chemical and physical properties for liposomal formulations of anticancer drugs not only with respect to the agent being encapsulated but also the specific clinical applications for which they will be used. This approach is not only applicable for conventional and sterically stabilized liposomal formulations but should also be applied for more complex multifunctional **liposomes**.

2000

17/3,AB/13 (Item 2 [redacted]m file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12519184 BIOSIS NO.: 200000272686
Tumor uptake and therapeutic effects of drugs encapsulated in long-circulating pegylated STEALTH(R) **liposomes**.
AUTHOR: Colbern Gail(a); Vaage Jan; Donovan Dorothy; Uster Paul; Working Peter
AUTHOR ADDRESS: (a)ALZA Corporation, 1900 Charleston Road, Mountain View, CA, 94039**USA
JOURNAL: Journal of Liposome Research 10 (1):p81-92 Feb., 2000
MEDIUM: print.
ISSN: 0898-2104
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: In this study, **tumor** uptake and clearance of **doxorubicin** were determined for two formulations of the drug: the free form in aqueous solution and the encapsulated form in polyethylene glycol-coated (pegylated, STEALTH(R)) **liposomes** composed of cholesterol/hydrogenated soy phosphatidylcholine/polyethylene glycol-distearoyl-phosphatidyl-ethanolamine (Doxil(R)). The determinations used confocal laser scanning microscopy in a pancreatic carcinoma model in nude mice. The movement of pegylated **liposomes** containing **doxorubicin** from blood vessels into **tumors** was studied using confocal microscopy combined with autoradiography of **liposomes** containing a tritium-labeled phospholipid. Laser microscopy measurements showed that the **liposome**-encapsulated **doxorubicin** remained in the **tumor** longer than the free drug and produced a six-fold increase in the area under the concentration-time curve (AUC). Autoradiography showed that the extravasated tritium-labeled lipid had entered the nuclei as well as the cytoplasm of **tumor** cells. The authors also compared the therapeutic effects of intravenous cisplatin, **doxorubicin** hydrochloride, **vincristine** sulfate, and vinorelbine tartrate, each in the aqueous free from or encapsulated in pegylated **liposomes**. In this pancreatic carcinoma model, the **liposome**-encapsulated drugs were all more effective than the free drugs in inhibiting **tumor** growth and in producing cures. Except for cisplatin, all of the free drugs had toxic systemic side effects indicated by an average weight loss of 3 to 5%, which was recovered by 2 to 4 weeks after the last **treatment**. The **liposome** -encapsulated drugs did not cause weight loss.

2000

17/3,AB/14 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12339166 BIOSIS NO.: 200000092668
In vitro cellular accumulation and cytotoxicity of liposomal and conventional formulations of **daunorubicin** and **doxorubicin** in resistant K562 cells.
AUTHOR: Wang Yuying(a); Eksborg Staffan; Lewensohn Rolf; Lindberg Annika; Liliemark Eva
AUTHOR ADDRESS: (a)Department of Oncology-Pathology, Cancer Center Karolinska (CCK), R8:00, Karolinska Institute and Hospital, 171 76, Stockholm**Sweden
JOURNAL: Anti-Cancer Drugs 10 (10):p921-928 Nov., 1999
ISSN: 0959-4973

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Previous investigations have indicated the possibility to circumvent multidrug resistance (MDR) by incorporation of an anthracycline into **liposomes**. We examined the in vitro cytotoxicity and cellular drug accumulation of the anthracyclines **daunorubicin** and **doxorubicin** compared with the commercially available liposomal formulations DaunoXome(R) and Caelyx(R) in human myelogenous leukemia K562 cells. The drug-sensitive parental K562/K line was compared with the P-glykoprotein (P-gp)-expressing cell lines K562/Dnr and K562/Vcr. Two cell lines with reduced levels of topoisomerase II (K562/Nov and K562/Ida) were also included. The cytotoxicity was determined by fluorometric microculture cytotoxicity assay and the cellular drug levels were determined by high performance liquid chromatograghy. There was a strong inverse correlation between P-gp levels and celluar drug accumulation (rho=-0.83, p=0.04) and cytotoxicity (rho=-0.95, p=0.01) of **daunorubicin**. Also the cytotoxicity of DaunoXome and **doxorubicin** was related to P-gp levels (rho=-0.96, p=0.01 and rho=-0.90, p=0.07, respectively). Caelyx did not show any cytotoxic effect due to impaired cellular uptake of the pegylated **liposome**. Regardless of the P-gp levels of the **treated** cells, DaunoXome showed the same cytotoxic effect despite lower intracellular accumulation (range 22-47%), compared with conventional **daunorubicin**.

1999

17/3,AB/15 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11856991 BIOSIS NO.: 199900103100
Anti-HER2 immunoliposomes for targeted drug delivery.
AUTHOR: Park J W(a); Kirpotin D; Hong K; Colbern G; Shalaby R; Shao Y; Meyer O; Nielsen U; Marks J; Benz C C; Papahadjopoulos D
AUTHOR ADDRESS: (a)505 Parnassus Ave., Box 1270, San Francisco, CA 94143-1270**USA
JOURNAL: Medicinal Chemistry Research 8 (7-8):p383-391 1998
ISSN: 1054-2523
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RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Anti-HER2 immunoliposomes (ILs) combine the **tumor**-targeting properties of certain anti-HER2 monoclonal antibodies (MAb) with the pharmacokinetic and drug delivery properties of sterically stabilized **liposomes** (Ls). Anti-HER2 U-s efficiently bind to and internalize in HER2-overexpressing cells in vitro, resulting in intraceilular drug delivery. Localization studies in **tumor** xenograft models confirm that anti-HER2 ILs, unlike **liposomes**, internalize in **tumor** cells in vivo. Gold-loaded IL-s accumulate intracellularly in the cytoplasm of **tumor** cells, while **liposomes** lacking MAb targeting accumulate extracellularly or within macrophages. This novel mechanism of targeted, intracellular delivery may account for the significantly enhanced antitumor efficacy of anti-HER2 U-s in vivo. Therapy studies demonstrate that delivery of **doxorubicin** (dox) via anti-HER2 ILs-dox greatly increases the therapeutic index of dox, both by increasing antitumor efficacy and by reducing systemic toxicity. Anti-HER2 ILs-dox produce marked therapeutic results in multiple HER2-overexpressing **tumor** xenograft models, including growth inhibition, regressions, and cures. Anti-HER2 ILs-dox is significantly superior to all other relevant **treatment** conditions, including free

dox, liposomal dox, free MAb, and combinations. In addition to dox, anti-HER2 ILs can in principle be constructed for **tumor** targeted delivery of a wide variety of anticancer agents, including alternate small molecule chemotherapeutics, **antisense** oligonucleotides, and therapeutic genes.

1998

17/3,AB/16 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11301734 BIOSIS NO.: 199800083066
Folate-targeted **liposomes** for drug delivery.
AUTHOR: Lee Robert J(a); Low Philip S
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JOURNAL: Journal of Liposome Research 7 (4):p455-466 Nov., 1997
ISSN: 0898-2104
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The folate receptor has been identified as a marker for ovarian carcinomas and is also up-regulated in many other types of cancer. Folate-conjugation has been successfully applied in the **tumor** cell-selective targeting of **liposomes**. A long polyethyleneglycol (PEG) spacer between the targeting ligand (i.e. folic acid) and the **liposome** surface is required for receptor recognition. Ligand binding is compatible with the PEG-coating of the **liposomes** needed for prolonged systemic circulation. Folate-targeted **liposomes** have been shown to enhance the in vitro cytotoxicity of **liposomeentrapped doxorubicin** and **antisense** oligodeoxynucleotides to receptor-bearing **tumor** cells. Folate, as a targeting ligand, offers unique advantages over immunoliposomes, i.e., easy liposomal incorporation, low cost, high receptor affinity and **tumor** specificity, extended stability, and potential lack of immunogenicity.

1997

17/3,AB/17 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11073102 BIOSIS NO.: 199799694247
Immunoliposomes as targeted delivery vehicles for cancer therapeutics (Review).
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JOURNAL: International Journal of Oncology 11 (2):p325-332 1997
ISSN: 1019-6439
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Advances in **liposome** technology over the last decade has seen the development of stealth **liposomes** for drug delivery and cationic **liposomes** for gene delivery. Many of these **liposome** formulations are now in clinical trials for the **treatment** of a variety of malignancies. Whilst some clinical efficacy has been demonstrated, the goal of specific **tumor** targeting is yet to be

attained. For this reason, antibodies have been attached to the surface of **liposomes** to produce immunoliposomes. These **liposomes** have shown preferential binding to specific **tumor** cells in animal models. The construction of the immunoliposome, and in particular the optimal method of antibody coupling to its surface is, however, yet to be determined. Despite these difficulties, immunoliposomes have demonstrated anti-**tumor** properties, both in vitro and in vivo, and show great promise as targeted delivery vehicles for the **treatment** of cancer.

1997

17/3,AB/18 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09783428 BIOSIS NO.: 199598238346
Prophylaxis and Therapy of Mouse Mammary Carcinomas with **Doxorubicin** and **Vincristine** Encapsulated in Sterically Stabilised **Liposomes**.
AUTHOR: Vaage J(a); Donovan D; Loftus T; Uster P; Working P
AUTHOR ADDRESS: (a)Dep. Mol. Immunol., Roswell Park Cancer Inst., Buffalo, NY 14263**USA
JOURNAL: European Journal of Cancer 31A (3):p367-372 1995
ISSN: 0959-8049
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This study tested the prophylactic efficacies of **doxorubicin** hydrochloride and **vincristine** sulphate, encapsulated in sterically stabilized long circulating **liposomes**, against the spontaneous development of mammary carcinomas in C3H/He mice. Monthly prophylactic intravenous (i.v.) injections of 6 mg/kg doses of **liposome**-encapsulated **doxorubicin** (DOX-SL) or 1 mg/kg doses of **liposome**-encapsulated **vincristine** (VIN-SL) were begun when retired breeding mice were 26 weeks old. Mice that developed a mammary carcinoma while on the monthly prophylactic protocols were then given weekly i.v. injections of 6 mg/kg DOX-SL or 1 mg/kg VIN-SL to test the therapeutic efficacies of the drugs, and to determine whether the tumours were susceptible or resistant to therapy. The monthly prophylactic injections reduced the incidence of first mammary carcinomas from 87/88 (99%) in untreated mice to 24/42 (57%) in DOX-SL-**treated** mice and to 26/32 (81%) in VIN-SL-**treated** mice. Of the mice that developed a mammary tumour while on the prophylactic protocols, 12 of 30 mice were cured by the weekly therapeutic use of DOX-SL, and the growth of 18 tumours was inhibited. The weekly therapeutic use of VIN-SL cured 3 of 8 mice, and inhibited the growth of five tumours. Weekly DOX-SL therapy cured 7 of 22 previously untreated mice. The mean survival of tumour-bearing mice was extended from 24 days in untreated mice to 87 days in DOX-SL-**treated** mice, which had not received prophylactic **treatment**. Metastases were found in 29 of 54 untreated mice, and in 3 of 72 mice **treated** with DOX-SL and VIN-SL. Toxic side effects were limited to a transient weight loss during the weekly **treatments**. Drug resistance as a result of **treatments** was not observed.

1995

17/3,AB/19 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

11275339 EMBASE No: 2001278988

the development of resistance to continued Bcl-2 ODN **treatment**. The antitumor activity of O[redacted] given in conjunction with eith[redacted]F- DOX or SL-DOX was also examined. The combination of G3139 and F-DOX was able to suppress the growth of MDA435/LCC6 cells beyond that obtained with either of the **treatments** given alone, indicative of synergistic action. Examination of the pharmacokinetics of F-DOX with systemic G3139 administration revealed that elevated **tumor** drug DOX levels were obtained compared with DOX **treatment** in the absence of G3139. This effect was sequence-specific and plasma DOX levels were unaffected by G3139 **treatment**, which indicated possible positive ODN-drug interactions at the **tumor** site. Combining G3139 with SL-DOX further increased the degree of antitumor activity. The improved efficacy of this combination was attributed to increased **tumor** drug levels that arise from the ability of SL-DOX to passively accumulate in solid **tumors**. These results suggest that additional benefits of Bcl-2 **antisense** ODN may be obtained when it is combined with liposomal formulations of anticancer drugs such as DOX.

17/3,AB/23 (Item 5 from file: 72)
DIALOG(R)File 72:EMBASE

07893954 EMBASE No: 1999361592
Anticancer therapy using glucuronate modified long-circulating **liposomes**
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AUTHOR EMAIL: oku@u-shizuoka-ken.ac.jp
Advanced Drug Delivery Reviews (ADV. DRUG DELIV. REV.) (Netherlands) 1999, 40/1-2 (63-73)
CODEN: ADDRE ISSN: 0169-409X
PUBLISHER ITEM IDENTIFIER: S0169409X9900040X
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 40

Since conventional **liposomes** tend to be trapped by the reticuroendothelial systems (RES), their use as drug carriers is limited when the targets are not RES cells. Therefore, many attempts have been made to avoid the RES-trapping of **liposomes**. Favorable results were obtained by a modification of **liposomes** with a glucuronic acid derivative, PGlcUA, and polyethyleneglycol. These **liposomes** have a long-circulating character, and showed the further advantage for passive targeting to **tumor** tissues, since the vasculature in **tumor** tissues is leaky enough for small-sized **liposomes** to extravasate. Thus long-circulating **liposomes** are useful for **tumor** imaging and **treatment**. PGlcUA-modified **liposomes** were actually found to accumulate effectively in **tumor** tissue, and showed enhanced efficacy of antitumor agents, such as adriamycin and **vincristine** when they were encapsulated into the **liposomes**. Usefulness of PGlcUA **liposomes** as drug carriers was also observed in photodynamic therapy and in **treatment** of cancer by amphiphilic novel antitumor agents.

17/3,AB/24 (Item 6 from file: 72)
DIALOG(R)File 72:EMBASE

07756156 EMBASE No: 1999239277
Transferrin as a targeting ligand for **liposomes** and anticancer drugs
Singh M.
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FL 32307 United States
Current Pharmaceutical [redacted]sign (CURR. PHARM. DES.) (Ne[redacted]rlands) 1999, 5/6 (443-451)
CODEN: CPDEF ISSN: 1381-6128
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 51

In cancer **treatment**, one of the approaches is targeting of the drug to **tumor** cells via receptor specific ligands. Transferrin (molecular weight 80,000) has been used as a ligand for delivering anticancer drugs or drug containing **liposomes** mostly due to the increased number of transferrin (trf) receptors found on **tumor** cells as compared to normal cells. Transferrin was linked to methotrexate (MTX) containing small unilamellar **liposomes** and its activity was compared to antitransferrin receptor antibody (7D-3) linked to MTX **liposomes**. In each of these conjugates, the method of coupling was the same and a disulphide linkage was formed between the ligand and MTX **liposomes**. No significant differences in the potency of 7D-3 conjugate or trf conjugate with MTX **liposomes** were observed in studies performed in vitro against various human **tumor** cell lines (Hela, KB and Colon). Trf was also linked to adriamycin via a schiff base which was formed by using glutaraldehyde. This conjugate was found to be effective in vitro against various human **tumors** (Lovo, HL-60, SW 403 and Hep2) and also in vivo against H-mesothelioma **tumors**. Transferrin receptor has also been used for gene delivery. Gene delivery to K562 haematopoietic leukaemic cells was achieved by using a transferrin-polycation (poly-L-lysine or protamine) conjugate. This review will cover the various important applications of transferrin based drug delivery formulations in the chemotherapy of cancer and the related work performed in our and other laboratories.

17/3,AB/25 (Item 7 from file: 72)
DIALOG(R)File 72:EMBASE

07465191 EMBASE No: 1998390862
Liposomal drug formulations: Rationale for development and what we can expect for the future
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Drugs (DRUGS) (New Zealand) 1998, 56/5 (747-756)
CODEN: DRUGA ISSN: 0012-6667
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 76

Liposomes are versatile drug carriers which can be used to solve problems of drug solubility, instability and rapid degradation. Both hydrophilic and hydrophobic drugs can be associated with **liposomes** and special techniques have been developed for the efficient loading of weak acids and weak bases into **liposomes**. **Liposomes** can function as sustained release systems for drugs and the rate of release can be manipulated. Advantage can be taken of the substantial changes in pharmacokinetics which often accompanies the association of drugs with **liposomes**. New formulations of **liposomes**, sterically stabilised with substances like surface-grafted polyethylene glycol have circulating half-lives in humans of up to 2 days. These long circulation times allow concentration of liposomal drug in regions of increased vascular permeability like solid tumours an decreased delivery of drug to normal tissues. Alterations of the biodistribution of drugs, when they are **liposomes**-associated, in general leads to significant overall

decreases in drug toxicity but can also increase toxicity in some tissues. The use of targeting ligands to increase the selectivity of delivery of liposomal drugs to target tissues is currently under development. An understanding of how **liposome** association can alter drug properties can lead to their rational development in the **treatment** of many diseases.

17/3,AB/26 (Item 8 from file: 72)
DIALOG(R)File 72:EMBASE

07409005 EMBASE No: 1998287659
Future developments in the selectivity of anticancer agents: Drug delivery and molecular target strategies
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Cancer and Metastasis Reviews (CANCER METASTASIS REV.) (Netherlands) 1998, 17/2 (211-218)
CODEN: CMRED ISSN: 0167-7659
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 32

In the past, our limited understanding of the processes involved in the initiation and growth of cancer hindered our ability to effectively **treat** most human malignancies and therapies were often associated with significant toxic side effects as well as re-emergence of disease. The development of drug delivery systems such as **liposomes** has improved the specificity of various conventional anticancer agents by enhancing drug accumulation in **tumors** while often decreasing exposure to susceptible healthy tissues. More recently, the identification of a wide range of genes and corresponding protein products that are altered in various human cancers has revealed new molecular targets for cancer therapy that may provide improved selectivity for **tumor** cells over traditional cytotoxic agents. This review discusses how advances in the sophistication of liposomal delivery systems may open new opportunities for combining novel molecular targeting strategies with pharmacological targeting via **liposomes** to optimize the therapy of many human malignancies.

17/3,AB/27 (Item 9 from file: 72)
DIALOG(R)File 72:EMBASE

07355183 EMBASE No: 1998212515
Acquired immune deficiency syndrome and malignancies
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Seminars in Colon and Rectal Surgery (SEMIN. COLON RECTAL SURG.) (United States) 1998, 9/2 (131-148)
CODEN: SCRSF ISSN: 1043-1489
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 152

With the rapid scientific advances in the antiretroviral therapy and pathogenesis of human immunodeficiency virus (HIV), the median life expectancy of HIV-infected patients has changed significantly, reaching more than 12 years. The unexpected consequence of this improved survival was a rise in the incidence of malignancies in HIV-infected patients. Although only three malignancies (Kaposi's sarcoma [KS], intermediate and high-grade non- Hodgkin's B-cell lymphoma [NHL], and cervical carcinoma)

have been conclusively associated with HIV infection and are considered as acquired immune deficiency virus syndrome (AIDS) defining conditions, other malignancies might be associated with AIDS as well. The course of malignancies in HIV-infected patients might be significantly affected by the HIV-induced immunosuppression and by several identified oncogenic viruses. Both the diagnosis and **treatment** of neoplastic diseases have to be approached quite differently in HIV-infected patients. Their management is a major challenge and requires a multidisciplinary approach to maintain maximum suppression of the replication of HIV and control the malignancy. Despite modest therapeutic advances, optimal therapy has not been defined for the majority of these neoplasms and their **treatment** remains a subject of controversy.

17/3,AB/28 (Item 10 from file: 72)
DIALOG(R)File 72:EMBASE

07069758 EMBASE No: 1997351621
Anthracyclines in the **treatment** of cancer. An overview
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Drugs (DRUGS) (New Zealand) 1997, 54/SUPPL. 4 (1-7)
CODEN: DRUGA ISSN: 0012-6667
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 53

Anthracyclines are widely used and effective antineoplastic drugs. Although active against a wide variety of solid tumours and haematological malignancies, their clinical use is hindered by tumour resistance and toxicity to healthy tissue. Modification of the general anthracycline ring structure results in analogues with different but overlapping antitumour and tolerability profiles. Activity of the anthracyclines is related to topoisomerase II inhibition, which occurs as a result of anthracycline intercalation between adjacent DNA base pairs. Production of hydroxyl free radicals is associated with antitumour effects and toxicity to healthy tissues. Myocardial tissue is particularly susceptible to free radical damage. Development of tumour cell resistance to anthracyclines involves a number of mechanisms, including P-glycoprotein-mediated resistance. The classical dose-limiting adverse effects of this class of drugs are acute myelosuppression and cumulative dose-related cardiotoxicity. Anthracycline-induced cardiomyopathy is often irreversible and may lead to clinical congestive heart failure. Other toxicities of the anthracyclines, including stomatitis, nausea and vomiting, alopecia and 'radiation recall' reactions, are generally reversible. Anthracycline-induced cardiotoxicity may be reduced or prevented by an administration schedule that produces low peak plasma drug concentrations. Administration of dexrazoxane also provides cardioprotection. Dose intensification of anthracyclines may partly overcome resistance but is associated with reduced tolerability. Liposomal encapsulation of **doxorubicin** or **daunorubicin** alters the pharmacokinetic properties of the drugs. Increased distribution in tumours, prolonged circulation and reduced free drug concentrations in plasma may increase antitumour activity and improve the tolerability of the anthracyclines.

17/3,AB/29 (Item 11 from file: 72)
DIALOG(R)File 72:EMBASE

07064639 EMBASE No: 1997346502
Challenges in the management of bone **tumors** - 1996
Craft A.W.

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Annals of the New York Academy of Sciences (ANN. NEW YORK ACAD. SCI.) (United States) 1997, 824/- (167-179)
CODEN: ANYAA ISSN: 0077-8923
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 34

17/3,AB/30 (Item 12 from file: 72)
DIALOG(R)File 72:EMBASE

07049405 EMBASE No: 1997331249
Future prospects for stealth **liposomes** in cancer therapy
Martin F.J.
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ONCOLOGY (ONCOLOGY (USA)) (United States) 1997, 11/10 SUPPL. 11 (63-68)
CODEN: OCLGE ISSN: 0890-9091
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 23

While **doxorubicin** (Adriamycin) is among the most active single agents in the **treatment** of breast cancer and other solid **tumors**, its concomitant toxicity limits its use. Quality-of-life issues have driven the search for gentler, palliative **treatments**, especially for use in the frail and the elderly populations. Pegylated liposomal **doxorubicin** (PEG-LD) (Doxil) is being tested in various combinations to develop such a **treatment** regimen. Antitumor activity in mice was seen when PEG-LD was combined with the anti- EGFr monoclonal antibody C225, supporting its use in combination with biologicals. Clinical studies are also underway that combine PEG-LD with either vinorelbine (Navelbine), gemcitabine (Gemzar), or paclitaxel (Taxol), which are chemotherapeutic agents with non-overlapping toxicities compared with PEG-LD. In addition, a pegylated liposomal form of cisplatin (Platinol) is being tested in animal **tumor** models. Early evidence suggests that dosing regimens can be optimized so that such combinations provide antitumor activity comparable with conventional combination regimens but with acceptable toxicity.

17/3,AB/31 (Item 13 from file: 72)
DIALOG(R)File 72:EMBASE

07049399 EMBASE No: 1997331243
Pegylated liposomal **doxorubicin**: Scientific rationale and preclinical pharmacology
Martin F.J.
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ONCOLOGY (ONCOLOGY (USA)) (United States) 1997, 11/10 SUPPL. 11 (11-20)
CODEN: OCLGE ISSN: 0890-9091
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 65

Liposome-encapsulated drag delivery is a methodology that has been evolving over the past 30 years. A number of **liposome**-encapsulated anthracycline products are in development and two, pegylated liposomal

doxorubicin (PEG-LD) (Doxil) and liposomal daunorabicin (Dauno-Xome), are approved for the **treatment** of AIDS-related Kaposi's sarcoma. Preclinical studies show PEG-LD to be at least as effective as traditional or 'free' **doxorubicin** (Adriamycin) in a variety of **tumor** models. Pharmacokinetic studies reveal differences between PEG-LD and **doxorubicin**, with PEG-LD having a higher area under the concentration-time curve (AUC), lower clearance rate, and smaller volume of distribution. In addition, PEG-LD was found to selectively accumulate in cutaneous Kaposi's sarcoma lesions of AIDS-infected individuals when compared with adjacent normal skin. Accumulating data have led to a proposed mechanism of PEG-LD accumulation in **tumors**: long-term circulating **liposomes** pass through gaps/defects in newly formed blood vessels and enter the **tumor** interstitium. **Liposome** breakdown within **tumors** releases **doxorubicin** molecules that travel deeper into the **tumor**, bind to nucleic acids, and result in **tumor**-cell killing. The ability of PEC-LD **liposomes** to remain intact while in circulation, retaining most of the **doxorubicin** in encapsulated formulation, is believed to be responsible for the reduced toxicity seen with this agent without sacrificing efficacy.

17/3,AB/32 (Item 14 from file: 72)
DIALOG(R)File 72:EMBASE

07022120 EMBASE No: 1997312816
Treatment of epidemic (AIDS-related) Kaposi's sarcoma
Jie C.; Tulpule A.; Zheng T.; Masood R.; Espina B.; Gill P.S.
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Current Opinion in Oncology (CURR. OPIN. ONCOL.) (United States) 1997, 9/5 (433-439)
CODEN: CUOOE ISSN: 1040-8746
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 38

Kaposi's sarcoma (KS) is the most common **tumor** seen in patients with HIV-1 infection, KS causes significant morbidity and mortality through involvement of the skin and visceral organs. The optimal **treatment** for KS depends on the extent of the disease and immunologic status. However, with knowledge gained on the pathogenesis of disease, newer therapies and compounds are being developed. Early disease patients are best **treated** with either local therapy or agents that have low toxicity and can be delivered long term. Advanced disease, such as in patients with widespread mucocutaneous disease, lymphedema, and visceral disease, are **treated** most effectively with cytotoxic agents such as liposomal anthracyclines, vinca alkaloids, or paclitaxel. Future **treatment** developments are focusing on the role of effective anti-HIV therapy and anti-human herpesvirus (HHV)-8 therapy in an effort to interfere with key steps in the etiology of KS to control the disease. Secondly, agents that focus on the interruption of autocrine and paracrine growth factors such as vascular endothelial cell growth factor and basic fibloblast growth factor, interleukin-6, and interleukin-8 are of therapeutic interest. Some of these compounds currently under evaluation include antiangiogenesis inhibitors and retionids.

17/3,AB/33 (Item 15 from file: 72)
DIALOG(R)File 72:EMBASE

06797038 EMBASE No: 1997078549
The design and development of DaunoXome(R) for solid **tumor** targeting in vivo

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Advanced Drug Delivery Reviews (ADV. DRUG DELIV. REV.) (Netherlands) 1997, 24/2-3 (133-150)
CODEN: ADDRE ISSN: 0169-409X
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DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 107

This article reviews the formulation development and characterization of the **tumor**-targeting **daunorubicin liposome** preparation, DaunoXome(R). The identification of **liposome** formulations capable of delivering their contents to solid **tumors** in vivo was contingent upon the development of an active loading technique for entrapping the gamma emitter, sup 1sup 1sup 1In. Using sup 1sup 1sup 1labeled **liposomes**, various formulations were screened for their ability to deliver entrapped materials to solid **tumors** selectively. With this sup 1sup 1sup 1In labeling approach, a wide range of compositions and physical characteristics (size, phase transition temperature, surface charge, etc.) were evaluated for their abilities to remain intact in the circulation for prolonged periods as well as to deliver and release their entrapped contents selectively within solid **tumors** in vivo. We identified as particularly effective, a formulation of distearolyphosphatidylcholine (DSPC) and cholesterol in a 2:1 mole ratio with diameters less than 100 nm. In clinical studies involving nearly 400 patients, these **liposomes** imaged a wide variety of primary cancers and their metastases. Classes of **tumors** successfully imaged include: breast, prostate, colon, kidney, cervix, thyroid, larynx, lung (small cell and non-small cell), lymphomas (malignant and Hodgkin's), sarcomas (soft tissue and Kaposi's). This basic formulation served as a model for development of a **liposome** delivery system to target antineoplastic agents to solid **tumors** in vivo. It had been know for some time that the formulation of anthracyclines into **liposomes** could be particularly advantageous for improving the therapeutic benefits of this drug class. For reasons discussed below, we selected **daunorubicin** over other anthracyclines for **liposome** development. The resulting **daunorubicin liposome** product, (DaunoXome(R)) is a formulation of **daunorubicin** in small unilamellar vesicles (SUVs) composed of highly pure distearoylphosphatidylcholine (DSPC) and cholesterol in a 2:1 mole ratio. Several countries, including the United States, have approved DaunoXome(R) for use in for **treating** Kaposi's sarcoma (KS) in HIV-positive patients. As with the sup 1sup 1sup 1In **tumor** imaging **liposomes**, we believe that DaunoXome(R) extravasates selectively into solid **tumors** through discontinuities in the capillary beads arising in **tumor** neovasculature. Preclinical investigations have indicated that DaunoXome(R) increases in vivo **daunorubicin tumor** delivery by about 10-fold over conventional drug, yielding a comparable increase in therapeutic efficacy. Investigations on the modes of delivery and of action indicate that DaunoXome(R) arrives at and accumulates within **tumor** cells primarily in an intact form. Once within the **tumor** cells, the **liposomes** release drug over a prolonged period (36 h or more), providing sustained, high levels of cytotoxic material within **tumor** cells. HIV-positive patients tolerate DaunoXome(R) well and their responses to it compare favorably with the typical therapy of ABV (**doxorubicin**, bleomycin, **vincristine**), demonstrating reduced toxicity while retaining comparable to improved antitumor activity. In this review, we report on issues of DaunoXome(R)'s formulation development and it's preclinical and clinical investigations.

17/3,AB/34 (Item 16 from file: 72)
DIALOG(R)File 72:EMBASE

06701618 EMBASE No: [redacted]6366565
Therapeutic opportunities for targeted liposomal drug delivery
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Advanced Drug Delivery Reviews (ADV. DRUG DELIV. REV.) (Netherlands) 1996, 21/2 (117-133)
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DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

One way to increase the therapeutic index of drugs such as anticancer drugs, which have low therapeutic indices would be by specifically targeting the drugs to the diseased cells. This can be accomplished by associating the drugs with **liposomes** and coupling a targeting antibody or ligand to the **liposome** surface. A variety of coupling methods can be used to attach antibodies or ligands to the **liposomes**, and, to date, the best targeting results have been obtained when the targeting moiety is attached at the terminus of a hydrophillic polymer such as polyethylene glycol (PEG). Targeted **liposomes** have been demonstrated to have specific binding and increased cytotoxicity to cells in vitro compared to non-targeted **liposomes**. The best therapeutic results in vivo have been obtained to date when the **liposomes** are targeted to cells easily accessible within the vasculature, or to micrometastatic cells. **Treatment** of more advanced solid tumours with targeted **liposomes** presents a challenge to overcome the 'binding site barrier' at the tumour surface. Evidence is accumulating that targeting to internalizing receptors is more successful than targeting to non-internalizing receptors.

17/3,AB/35 (Item 17 from file: 72)
DIALOG(R)File 72:EMBASE

06623774 EMBASE No: 1996288571
Chemotherapy of AIDS-related Kaposi's sarcoma
Lee F.-C.; Mitsuyasu R.T.
UCLA CARE Center, 10833 Le Conte Avenue,Los Angeles, CA 90095-1793 United States
Hematology/Oncology Clinics of North America (HEMATOL. ONCOL. CLIN. NORTH AM.) (United States) 1996, 10/5 (1051-1068)
CODEN: HCNAE ISSN: 0889-8588
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Kaposi's sarcoma (KS) is the most common **tumor** associated with AIDS. A growing number of patients with this **tumor** are presenting at later stages of HIV with more rapidly progressive, extensive, or symptomatic KS or with **tumors** involving visceral organs. Chemotherapy **treatment** is effective in inducing **tumor** regression, reducing edema, and ameliorating symptoms caused by these **tumors**. Side effects and toxicities from these agents, however, can be quite pronounced, especially in patients with advanced AIDS. Antiretroviral therapy, prophylaxis for opportunistic infections, and the use of hematopoietic growth factors should be routinely included in the management of these patients. Newer chemotherapeutic agents and combination regimens may be more effective or less toxic than previously evaluated regimens.

17/3,AB/36 (Item 18 from file: 72)
DIALOG(R)File 72:EMBASE

06400025 EMBASE No: 6056163
Doxorubicin encapsulated in **liposomes** containing surface-bound polyethylene glycol: Pharmacokinetics, **tumor** localization, and safety in patients with AIDS-related Kaposi's sarcoma
Northfelt D.W.; Martin F.J.; Working P.; Volberding P.A.; Russell J.; Newman M.; Amantea M.A.; Kaplan L.D.
Pacific Oaks Medical Group, 8730 Wilshire Blvd.,Beverly Hills, CA 90211 United States
Journal of Clinical Pharmacology (J. CLIN. PHARMACOL.) (United States) 1996, 36/1 (55-63)
CODEN: JCPCB ISSN: 0091-2700
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

A study of the plasma pharmacokinetics, **tumor** localization, and safety of a single dose of **doxorubicin** encapsulated in **liposomes** containing surface- bound polyethylene glycol (PEG-liposomal **doxorubicin**) was conducted in patients with Kaposi's sarcoma (KS) as a manifestation of acquired immune deficiency syndrome (AIDS). Eighteen patients with AIDS-KS diagnosed by examination of biopsy specimens were randomly assigned to receive either standard **doxorubicin** or PEG-liposomal **doxorubicin**. Consecutive participants were entered at three dose levels (10, 20, and 40 mg/msup 2) in ascending fashion. Clearance of PEG-liposomal **doxorubicin** was 0.034 L/h/msup 2 to 0.108 L/h/msup 2, volume of distribution (Vd) was 2.2 L/msup 2 to 4.4 L/msup 2, and half- lives (t1/2) of the initial decline in the plasma concentration-time curve and of the terminal decline were 3.77 hours and 41.3 hours, respectively. Seventy-two hours after administration, **doxorubicin** levels observed in lesions of patients receiving PEG-liposomal **doxorubicin** were 5.2 to 11.4 times greater than those found in patients given comparable doses of standard **doxorubicin**. PEG-liposomal **doxorubicin** and standard **doxorubicin** were roughly equipotent in producing toxicity. Encapsulation in **liposomes** containing surface-bound PEG significantly limits the distribution and elimination of **doxorubicin**, results in greater accumulation of the drug in KS lesions 72 hours after dosing than does standard **doxorubicin**, and may improve drug efficacy and therapeutic index in the **treatment** of AIDS-KS.

17/3,AB/37 (Item 19 from file: 72)
DIALOG(R)File 72:EMBASE

05940992 EMBASE No: 1994348570
Phase I and pharmacologic study of liposomal **daunorubicin** (DaunoXome)
Guaglianone P.; Chan K.; DelaFlor-Weiss E.; Hanisch R.; Jeffers S.; Sharma D.; Muggia F.
Division of Medical Oncology, University of Southern California, P.O. Box 33800,Los Angeles, CA 90033-0800 United States
Investigational New Drugs (INVEST. NEW DRUGS) (United States) 1994, 12/2 (103-110)
CODEN: INNDD ISSN: 0167-6997
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

We have completed a phase I and pharmacology study of liposomally-encapsulated **daunorubicin** (DaunoXome). Of 32 patients entered, 30 were evaluable. No toxicity was encountered at the initial dose-escalation steps from 10 to 60 mg/msup 2. At 80 mg/msup 2, two patients manifested grade 2 neutropenia. At least grade 3 neutropenia occurred in all patients receiving 120 mg/msup 2. Alopecia and subjective intolerance were mild. Cardiotoxicity was not observed except for an episode of arrhythmia in a

patient with lung cancer and prior radiation. Only one minor objective response was observed in this population of refractory solid **tumors**. Pharmacokinetics differed from those of the free drug with no detection of daunorubicinol. We recommend future phase II studies with a dose of 100 mg/msup 2 in previously **treated** and 120 mg/msup 2 of DaunoXome in previously untreated patients with solid **tumors**.

17/3,AB/38 (Item 20 from file: 72)
DIALOG(R)File 72:EMBASE

05848459 EMBASE No: 1994239350
Endemic Kaposi's sarcoma - etiopathogenesis, epidemiology, clinical presentation and therapy
DAS ENDEMISCHE KAPOSI-SARKOM. ATIOPATHOGENESE, EPIDEMIOLOGIE, KLINIK UND THERAPIE
Plettenberg A.; Meigel W.
Lohmuhlenstrasse 5,D-20099 Hamburg Germany
Allergologie (ALLERGOLOGIE) (Germany) 1994, 17/7 (295-302)
CODEN: ALLRD ISSN: 0344-5062
DOCUMENT TYPE: Journal; Review
LANGUAGE: GERMAN SUMMARY LANGUAGE: GERMAN; ENGLISH

This article reviews the pathogenesis, epidemiology, clinical presentation, staging classifications, and **treatment** of Kaposi's sarcoma. The pathogenesis of the HIV-associated Kaposi's sarcoma is still unclear. Epidemiologic observations suggest that Kaposi's sarcoma may be caused by an infectious agent, transmitted by sexual contact. Several groups have been shown that in cell culture cytokines can stimulate the development and growth of Kaposi's sarcoma. Although the most common localization of this **tumor** is the skin, all organs may be affected. Involvement of the lung and gastrointestinal tract is common and may often result in profoundly clinical symptoms. Both local and systemic therapeutic measures are available. In systemic therapy interferons may be used alone or in combination with nucleoside analogues. In progressive Kaposi's sarcoma cytostatic agents are often required.

17/3,AB/39 (Item 1 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00119477

Medical Progress: Common Musculoskeletal **Tumors** of Childhood and Adolescence (Review Article)

Arndt, Carola A.S.; Crist, William M.
The New England Journal of Medicine
Jul 29, 1999; 341 (5),pp 342-352
LINE COUNT: 00592 WORD COUNT: 08180

17/3,AB/40 (Item 2 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00118487

Current Concepts: **Doxorubicin** -Induced Cardiomyopathy (Review Articles)

Singal, Pawan K.; Iliskovic, Natasha.
The New England Journal of Medicine
Sep 24, 1998; 339 (13), pp 900-905
LINE COUNT: 00418 WORD COUNT: 05777

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? s acid (w) glycoprotein

         2525888  ACID
          168132  GLYCOPROTEIN
      S1    6718  ACID (W) GLYCOPROTEIN
? s s1 and alpha (w) 1

Processing
            6718  S1
         1109033  ALPHA
         6301851  1
           92110  ALPHA(W)1
      S2    5048  S1 AND ALPHA (W) 1
? s s2 and liposom?

            5048  S2
           59517  LIPOSOM?
      S3      19  S2 AND LIPOSOM?
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...completed examining records
      S4      12  RD (unique items)
? t s4/3,ab/all


 4/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09533700   98030098   PMID: 9363647
   Kinetics and role of alpha 1-acid glycoprotein
-dependent osmotic transport of water and ions in palmitoyl-L-oleoyl
phosphatidylcholine liposomes.
  Neitchev V; Kostova E; Goldenberg M; Doumanova L
  Institute of Biophysics, Bulgarian Academy of Sciences, Sofia, Bulgaria.
  international journal of biochemistry & cell biology (ENGLAND)   Apr 1997
, 29 (4) p689-701, ISSN 1357-2725   Journal Code: CDK
  Languages: ENGLISH
  Document type: Journal Article
  Record type: Completed
  alpha 1-Acid glycoprotein isolated from human
blood plasma is known to influence cell permeability, although the
mechanisms of this process are unclear. Here, the glycoprotein effects on
the permeability of osmotically stressed phospholipid liposomes are
studied as a model of membrane permeability. Liposomes containing
glycoprotein were found to be osmotically sensitive to water and chloride
salts of some monovalent (Na+, K+) and bivalent (Mg2+, Ca2+) ions. The
permeations of these substances were determined by light-scattering
measurements of the volume changes in liposomes after mixing with
hyperosmotic solutions of chloride salts. The time courses of scattered
light were recorded by means of stopped-flow spectrophotometry. Two
processes were studied: the fast water outflow from liposomes and
slower ion permeations through the lipid membrane. The second order
permeation rate constants were determined at different glycoprotein
concentrations for both processes. Values from 66 to 250 x 10(3) for water
outflow and 2-500 M-1 sec-1 for the different ion permeations were obtained
in order to characterize the permeations of solutes across the lipid
membrane. The apparent activation energies also were calculated between 18
and 33 degrees C. The mercurial sulphydryl reagent pCMBS inhibited the ion
permeations in the slow phase. When pCMBS was present in this phase, higher
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activation energies were obtained, indicating more difficult permeations. An interpretation of these results is that membrane permeability is mediated by aqueous pores. Membrane selectivity to monovalent metal ions also was demonstrated, but no correlation was observed between the ion radius of the corresponding metal cation and permeation rate constants. The discovery of non-specific pores in **liposomes** containing glycoprotein shows that they can serve as vehicles for the water and ions in the processes of passive transport through lipid membranes.

4/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09495402 95217186 PMID: 7702604
A novel phosphatidylcholine hydrolysing action of C-reactive protein.
Mookerjea S; Hunt D
Department of Biochemistry, Memorial University of Newfoundland, St. John's, Canada.
Biochemical and biophysical research communications (UNITED STATES) Mar 28 1995, 208 (3) p1046-52, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We have observed a novel time and dose dependent stimulatory effect of CRP on the hydrolysis of dipalmitoyl phosphatidylcholine (DPPC) into phosphorylcholine (P-choline) and diacylglycerol (DAG). This effect was shared by rat, rabbit, human and asialo-rat CRP but not by other serum proteins, i.e., albumin, ovalbumin and **alpha 1-acid glycoprotein** . DPPC was also hydrolysed by normal rat serum (contains CRP) but not when serum was depleted of CRP. There is a requirement of Ca2+ for this unsuspected effect which was observed over a wide range of pH and the effect was markedly increased in temperatures up to 48 degrees C. The hydrolysis of DPPC showed a 3-fold decrease in Km when the assays included rat CRP. Massive increase of CRP in response to inflammation and its involvement in host defense reactions have been well documented. Significance of the present study rests on the possibility that the mechanism of action of CRP in cellular metabolism might be related to the production of DAG and P-choline known to have roles respectively in signal transduction and growth factor stimulated DNA synthesis.

4/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09486339 94347767 PMID: 8068669
Differential interactions of camptothecin lactone and carboxylate forms with human blood components.
Mi Z; Burke TG
Division of Pharmaceutics, College of Pharmacy, Ohio State University, Columbus 43210-1291.
Biochemistry (UNITED STATES) Aug 30 1994, 33 (34) p10325-36, ISSN 0006-2960 Journal Code: A0G
Contract/Grant No.: CA 63653, CA, NCI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The intrinsic fluorescent emissions from the lactone and carboxylate forms of camptothecin have been exploited in order to elucidate their markedly different interactions with the various components of human blood. In phosphate-buffered saline (PBS) at pH 7.4, human serum albumin (HSA) preferentially binds the carboxylate form with a 150-fold higher affinity than the lactone form; these interactions result in camptothecin opening more rapidly and completely in the presence of HSA than in the protein's absence [Burke, T.G., & Mi, Z. (1993) Anal. Biochem. 212, 285-287]. In human plasma, at pH 7.4 and 37 degrees C, we have observed camptothecin

lactone to open rapidly and fully to the carboxylate form (t1/2 = 11 min; % lactone at equilibrium, 2%). Substitution of a 10-hydroxy moiety into the camptothecin fluorophore makes the agent's emission spectrum highly sensitive to microenvironment polarity; we have observed pronounced blue shifting (from 530 to 430 nm) in the emission spectra of the hydroxy-substituted carboxylate both upon HSA association as well as upon drug dissolution in organic solvents of low dielectric strength. Hence, it appears that camptothecin carboxylate's fluorophore locates in a hydrophobic binding pocket in native HSA. Ionic interactions also appear to strongly affect binding between camptothecin carboxylate and the HSA binding pocket, since a 6-fold increase in solution salt concentration diminished camptothecin carboxylate binding by 10-fold. Our findings that HSA denaturation abolishes high-affinity binding indicate that interactions of the carboxylate drug form are specific for the native HSA conformation. Interestingly, high-affinity binding of the carboxylate appeared not to occur in the presence of other blood proteins, such as gamma-globulin, **alpha 1-acid glycoprotein**, fibrinogen, and the oxy
and deoxy forms of hemoglobin. In whole blood versus plasma, camptothecin was found to display enhanced stability (t1/2 value of 22 min and a lactone concentration at equilibrium value of 5.3%). The enhanced stability of camptothecin in human blood was found to be due to drug associations with the lipid bilayers of red blood cells. Camptothecin lactone partitions into the lipid bilayers of erythrocytes, with the drug locating in a hydrophobic environment protected from hydrolysis.

4/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09073670 96375684 PMID: 8781973
Biosynthesis in vitro of neolactotetraosylceramide by a galactosyltransferase from mouse T-lymphoma: purification and kinetic studies; synthesis of neolacto and polylactosamine core.
Basu M; Weng SA; Tang H; Khan F; Rossi F; Basu S
Department of Chemistry and Biochemistry, University of Notre Dame, IN 46556, USA.
Glycoconjugate journal (ENGLAND) Jun 1996, 13 (3) p423-32, ISSN 0282-0080 Journal Code: BJJ
Contract/Grant No.: CA33752, CA, NCI; NS-18005, NS, NINDS
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The galactosyltransferase, GalT-4, which catalyses the biosynthesis in vitro of neolactotetraosylceramide, nLcOse4Cer (Gal beta 1-4GlcNAc beta 1-3Gal beta 1-4Glc-Cer) from lactotriaosylceramide, LcOse3Cer (Glc NAc beta 1-3Gal beta 1-4Glc-Cer), and UDP-galactose has been purified 107 500-fold from a mineral oil induced mouse T-lyphoma P-1798, using affinity columns. The purified enzyme is partially stabilized in the presence of phospholipid **liposomes** . Two closely migrating protein bands of apparent molecular
weights 56 kDa and 63 kDa were observed after sodium dodecyl sulfate polyacrylamide gel electrophoresis of highly purified mouse GalT-4. These two protein bands, when subjected to limited proteolysis, resulted in three peptides with identical mobilities indicating amino acid sequence identity between the proteins. Both protein bands from P-1798 gave a positive immunostain when tested with polyclonal antibody against bovine lactose synthetase (UDP-Gal:Glc beta 4-galactosyltransferase) following Western blot analysis on nitrocellulose paper. The enzyme has a pH optimum between 6.5 and 7.0 and like all other galactosyltransferases, GalT-4 has absolute requirements for divalent cation (Mn2+). The K(m) values for the substrate LcOse3Cer and donor UDP-galactose are 110 and 250 microM, respectively. Substrate competition studies with LcOse3Cer and either asialo-agalacto-**alpha 1-acid glycoprotein** or N-acetylglucosamine
revealed that these reactions might be catalysed by the same protein. The only other glycolipid which showed acceptor activity toward the purified GalT-4 was iLcOse5Cer (GlcNAc beta 1-1-3Gal beta 1-4Lc3), the precursor for

polylactosamine antigens. However, competition studies with these two active substrates using the most purified enzyme fraction, revealed that these two reactions might be catalysed by two different proteins since the experimental values were closer to the theoretical values calculated for two enzymes. Interestingly however, it seems that the GalT-4 from P-1798 has an absolute requirement for an N-acetylglucosamine residue in the substrate since the lyso-derivative (GlcNH2 beta 1-3Gal beta 1-4Glc-sphingosine) of the acceptor glycolipid LcOse3Cer is completely inactive as substrate while the K(m) and Vmax of the reacetylated substrate (GlcNAc beta 1-3Gal beta 1-4Glc-acetylsphingosine) was comparable with LcOse3Cer. Autoradiography of the radioactive product formed by purified P-1798 GalT-4 confirmed the presence of nLcOse4Cer, as the product cochromatographed with authentic glycolipid. The monoclonal antibody IB-2, specific for nLcOse4Cer, also produced a positive immunostained band on TLC as well as giving a positive ELISA when tested with radioactive product obtained using a highly purified enzyme from mouse P-1798 T-lymphoma.

4/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08584127 95138039 PMID: 7530711
Carbohydrate-dependent binding of the cell-free hemagglutinin of Vibrio cholerae to glycoprotein and glycolipid.
Saha N; Banerjee KK
Division of Immunology and Vaccine Development, National Institute of Cholera and Enteric Diseases, Calcutta, India.
Journal of bacteriology (UNITED STATES) Feb 1995, 177 (3) p758-64, ISSN 0021-9193 Journal Code: HH3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The carbohydrate-binding specificity of the cell-free hemagglutinin (HA) of Vibrio cholerae (K.K. Banerjee, A.N. Ghose, K. Datta-Roy, S.C. Pal, and A.C. Ghose, Infect. Immun.58:3698-3705, 1990) was studied by using glycoconjugates with defined sugar sequences. The HA was not inhibited by simple sugars including glucobiose, galabiose, and their N-acetylated derivatives. The hemagglutination of rabbit erythrocytes by the HA was inhibited moderately by fetuin, calf thyroglobulin, and human **alpha 1-acid glycoprotein**, all of which contain multiple asparagine-linked complex-type oligosaccharide units alone or in combination with serine/threonine-linked oligosaccharide units. The inhibitory potencies of the glycoproteins increased approximately 10-fold following removal of the terminal sialic acid and were completely destroyed by exhausative proteolysis. The HA agglutinated phosphatidylcholine **liposomes** containing GM1-ganglioside or its asialo-derivative in the presence of Ca2+ ions. The association constants of the complexes of the HA with asialofetuin, asialothyroglobulin, GM1-ganglioside, and asialo-GM1-ganglioside were determined by an enzyme-linked immunosorbent assay-based assay and found to be 1.7 x 10(7) M-1, 1.5 x 10(7) M-1, 1.8 x 10(7) M-1, and 2.4 x 10(7) M-1, respectively. Studies using chemically modified glycoproteins and plant lectins with defined sugar specificity revealed that the HA recognized the terminal beta 1-galactosyl moiety of these glycoconjugates. There was no evidence for the presence of an extended carbohydrate-binding domain in the HA molecule or a preference of the HA for a complex, branched oligosaccharide structure.(ABSTRACT TRUNCATED AT 250 WORDS)

4/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06608655 89127167 PMID: 3221845
Temperature-dependent osmotic permeability in glycoprotein containing **liposomes**.

Neitchev VZ; Bideaud E[redacted]
Central Laboratory of [redacted]ophysics, Bulgarian Academy of [redacted]ences, Sofia.
Molecular biology reports (NETHERLANDS) 1988, 13 (2) p85-9, ISSN 0301-4851 Journal Code: NGW
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The osmotic water outflow of large multilamellar **liposomes** containing **alpha 1-acid glycoprotein** was measured at a temperature near the lipid's phase transition temperature. The **liposomes** were formed from a mixture of DPPC, cholesterol and glycoprotein in molar ratios 100:20:1, by continuous sucrose density gradient centrifugation. These **liposomes** captured 35% of the radiolabeled glycoprotein. The temperature-dependent experiments showed that near phase transition temperature the initial rate of water outflow increased drastically in comparison with glycoprotein free **liposomes** incubated in buffer containing glycoprotein. We suggested that eventual a channel mechanism may be involved due to spontaneous incorporation of glycoprotein into the bilayer.

4/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06601248 88122100 PMID: 3431542
Osmotic water permeability in glycoprotein containing **liposomes**.
Neitchev VZ; Kostadinov AP
Central Laboratory of Biophysics, Bulgarian Academy of Sciences, Sofia.
Molecular biology reports (NETHERLANDS) 1987, 12 (4) p253-8, ISSN 0301-4851 Journal Code: NGW
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The kinetics of osmotic water permeability in proteoliposomes containing **alpha 1-acid glycoprotein** was investigated by means of stopped-flow spectrophotometry. A biphasic time-course of scattered light with time was registered. The rate constants calculated from fits to an exponential function in the first phase were proportional to the final medium osmolarity. The apparent second order rate constants Kapp (Osm-1 sec-1) were determined at different glycoprotein concentrations in the original mixture for preparation of proteoliposomes. The value of Kapp at lipid:glycoprotein weight ratio = 1 was plotted in Arrhenius coordinates. The calculated activation energy for water permeation through the lipid bilayer suggests that eventual channel mechanism may be involved due to the presence of glycoprotein molecule in the **liposomes**.

4/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06073864 89386829 PMID: 2780633
Alpha 1-acid glycoprotein effects on the permeability changes in reconstituted membranes.
Neitchev VZ
Central Laboratory of Biophysics, Bulgarian Academy of Sciences, Sofia.
Progress in clinical and biological research (UNITED STATES) 1989, 300 p243-6, ISSN 0361-7742 Journal Code: PZ5
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

4/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06054815 86284603 PMID: 3736543
Osmotic water permeability through **liposomes** in the presence of **alpha 1-acid glycoprotein**.
Neitchev VZ; Jung WK
Molecular biology reports (NETHERLANDS) 1986, 11 (2) p87-92, ISSN 0301-4851 Journal Code: NGW
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Alpha 1-acid glycoprotein (orosomucoid) from human blood serum was isolated in pure form and then reconstituted into large multilamellar **liposomes** , consisting of a binary mixture of hen-egg phosphatidylcholine and cholesterol. These **liposomes** were found to be osmotically sensitive. The osmotic water permeability of proteoliposomes was determined by light-scattering measurements of the osmotic volume changes after mixing with hyperosmotic solutions of potassium salts and aminoglycoside antibiotics. The initial rate of water outflow was measured as a function of glycoprotein concentration in the mixture for the preparation of proteoliposomes. This can serve as an indication for membrane permeability to the solutes used in these experiments. It was shown that aminoglycoside antibiotics passed much faster across the membrane than potassium salts, in the presence of glycoprotein in the **liposomes**. A recognition pattern in the osmotic behavior of these proteoliposomes was assumed.

4/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04121183 82195215 PMID: 7078551
Glycoprotein-protein interaction examined by kinetic studies of pyrene transfer.
Neitchev VZ; Bideaud FA
Molecular biology reports (NETHERLANDS) Mar 31 1982, 8 (2) p65-9, ISSN 0301-4851 Journal Code: NGW
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The transfer of pyrene between **alpha 1-acid glycoprotein**, acethylcholinesterase and sonicated **liposomes** was used to monitor glycoprotein-protein interaction on the lipid bilayer. When a density solution of glycoprotein or protein labeled with pyrene was mixed with unlabeled suspension of free-phospholipid **liposomes** , or suspensions containing the complexes of glycoprotein-lipid, protein-lipid, or glycoprotein-protein-lipid, pyrene excimer fluorescence increased with a half-time of approximately 30--50 msec. Since the increase in excimer fluorescence indicates an increase in the microscope concentrations of pyrene, the observed fluorescence change reflects pyrene transfer. The half-times for the increase in excimer fluorescence were determined in the presence of glycoprotein and protein in the **liposomes**. On the basis of the determined half-times it was concluded that both, glycoprotein and protein are bound on the lipid bilayer. Our data also suggest that the thickness of the lipid bilayer is significantly changed in this case. The observation suggests strongly that the limiting step in the transfer of pyrene is not the dissociation of pyrene, but the uptake of the pyrene monomers by the lipid phase.

4/3,AB/11 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

04190431 BIOSIS NO.: 000077016475
GLYCO PROTEIN PROTEIN ASSOCIATED EFFECTS AND PERMEABILITY CHANGES IN RECONSTITUTED MEMBRANES

AUTHOR: NEITCHEV V Z; DESBALS B P
AUTHOR ADDRESS: CENT. LA[redacted] BIOPHYSICS, BULGARIAN ACAD. SC[redacted] 1113 SOPHIA, BULGARIA.
JOURNAL: INT J BIOCHEM 15 (8). 1983. 1085-1088. 1983
FULL JOURNAL NAME: International Journal of Biochemistry
CODEN: IJBOB
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The associated role of membrane constituents such as proteins and glycoproteins on **liposome** permeability was studied by the osmotic effects on phospholipid **liposomes** in the presence and absence of bound glycoprotein [human **.alpha.1-acid glycoprotein**]. As a measure of the permeability, the permeation time [.tau.) were obtained as a function of glycoprotein-protein molar ratio. The permeation times varied considerably with the change of glycoprotein-protein molar ratio in the **liposomes**. The topographical distribution of hydrophobic and hydrophylic regions of glycoproteins molecules may play a substantial role and influence the permeability. The distance of separation between both glycoprotein and protein molecules would change in this case which was confirmed by the method of fluorescence energy transfer.

1983

4/3,AB/12 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03498225 BIOSIS NO.: 000073001305
SEPARATION OF CELL SURFACE GLYCO PROTEINS FROM GLYCO LIPIDS BY RICINUS-COMMUNIS AGGLUTININ SEPHAROSE
AUTHOR: TSAO D; KIM Y S
AUTHOR ADDRESS: GASTROINTESTINAL RES. LAB. 151M2 , VETERANS ADM. MED. CENT., SAN FRANCISCO, CALIF. 94121.
JOURNAL: J BIOL CHEM 256 (10). 1981. 4947-4950. 1981
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The terminal galactosyl and N-acetylgalactosaminyl residues of the cell surface glycoconjugates of human cells were labeled in vitro by treating intact cells with galactose oxidase and sodium borotritide. Three types of human cells were used: red blood cells, colonic tumor cells and skin fibroblasts. The binding of the labeled surface components to the galactose and N-acetylgalactosamine specific lectin, Ricinus communis agglutinin (RCA), covalently coupled to Sepharose 4B, was examined. The cell membranes were solubilized in nonionic detergent; all labeled glycoproteins bound to the RCA-Sepharose column. Labeled membrane glycolipids containing terminal galactosyl or N-acetylgalactosaminyl residues did not bind to the lectin column. The lack of binding of glycolipids to the lectin is not dependent upon the concentration of detergent used to solubilize the membranes. Purified galactosyl-containing glycoproteins such as desialated **.alpha. 1-acid glycoprotein** and desialated ovine submaxillary mucin bound to RCA-Sepharose, while purified glycolipids such as gangliosides and globosides did not. **Liposomes** containing gal.beta.1 .fwdarw. 3GalNac.beta.1 .fwdarw. 4Gal(3 .rarw. 2.alpha.NeuAc).beta.1 .fwdarw. 4Glc.beta.1 .fwdarw. 1' Cer (GM1) ganglioside or Gal.beta.1 .fwdarw. 1' Cer (GL1b) globoside bound specifically to the RCA-Sepharose column. The lack of binding of solubilized glycolipids to the RCA-Sepharose column could be due to the fact that their monovalency results in too low an affinity for the lectin

to cause retention on the column. The observed differential binding properties of detergent solubilized cell surface glycoproteins and glycolipids to RCA-Sepharose columns can be used for the concentration and isolation of labeled membrane glycoproteins free from contamination